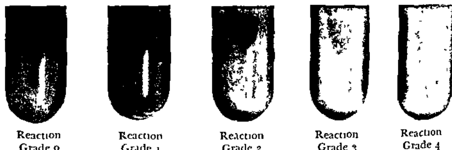
BENEDICT'S QUALITATIVE TEST FOR SUGAR IN THE URINE



Reaction Grade 0 | Reaction Grade 1 | Reaction Grade 2 | Reaction Grade 3 | Reaction Grade 4

The colored photographs above represent the appearance of solutions in test tubes containing 8 drops (0.4 c c) of urine added to 1 teaspoonful (5 c c) of Benedict's qualitative solution, the mixture being boiled for one minute over a free flame The urine added to the first tube on the left (Reaction grade 0) contained no sugar (dextrose) That added to the other tubes contained sugar (dextrose) in increasing concentrations from left to right Reaction grade 1 and reaction grade 2 represent reactions to traces of sugar (0 2 and 0 8 per cent, respectively) Reaction grade 3 and reaction grade 4 represent reactions with urine containing more than 1 per cent of sugar (1 5 and 4 per cent, respectively) (Wilder, R M A primer for diabetic patients Ed 6, Philadelphia W B Saunders Co, 1937, plate I)

CLINICAL DIABETES MELLITUS

and

HYPERINSULINISM

By

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To

my wife

LUCY ELIZABETH BEELER WILDER

in appreciation of encouragement

and assistance

PREFACE

The writer of a monograph, if the subject is one in which information is rapidly accumulating, runs the risk that formulation of his opinions may crystallize his thought and thus impair his responsiveness to new ideas This reflection has deterred me heretofore from venturing to prepare a book on diabetes, although this disease, for twenty-five years, has occupied the major part of my attention In 1915 I was taken into the Sprague Institute Laboratory in Rush Medical College and the Presbyterian Hospital of Chicago, where Rollin Woodyatt, recently returned from Friedrich Muller's clinic in Munich, was engaged in investigation of the intermediary metabolism of sugar. For nearly three years I was under his tutelage, and that of Frank Billings, with greater advantage, I believe, than could have been obtained at that time in any other environment. For this opportunity I am deeply grateful. In 1919, after the interlude of the war, I came to Rochester, and here since then, except for an interval of two years and a few months in the University of Chicago, I have been responsible continuously for the supervision of patients coming to The Mayo Clinic for treatment of diabetes, or coming with diabetes for medical or surgical treatment of other disease In the task I have been fortunate in receiving the best of guidance and co-operation, and for this I am deeply indebted to many colleagues and to William and Charles Mayo, whose wise direction created so effective an organization for the practice of modern medicine

Purposely omitted from this book is extensive consideration of the theory of carbohydrate metabolism, the physiology of experimental diabetes, and the pathology of diabetes. These topics now are so involved that a book on each subject, as large as this, would be required to present them comprehensively. Also excellent monographs covering them are readily available. My thesis is limited to clinical considerations, with the single purpose of describing procedure which in my experience and that of my associates has proved most effective in the recognition and treatment of the disease diabetes and its complications.

There is no reason to suppose that the existence of diabetes imparts immunity to any disease, therefore, in any large diabetic practice, every conceivable pathologic condition can be expected. In The Mayo Clinic in one year, 1937, among 1184 diabetic patients, the diseases associated with the diabetes numbered 153. Among the unusual associated conditions was one case each of gout, myasthenia gravis, polycystic kidney, protruded nucleus pulposus of intervertebral disks, marble bone disease, carotid sinus syndrome and temporal arteritis. There were two cases of tumor of the brain, two of tumor of the spinal cord, four of acromegaly, six of pernicious anemia, and so forth. The experience is mentioned to emphasize that physicians who propose to treat diabetes must be prepared to meet all of the exigencies of the broadest possible kind of a general practice. Many of the associated conditions are in no way related to diabetes; their occurrence is pure coincidence. Others are encountered with such disproportionate frequency that relationship or interdependence is suspected. Among the latter are the diseases of glands of internal secretion other than the pancreas, several abnormalities of the eye, the nervous system, the skin, the genitalia, the gastro-intestinal tract, the cardiovascular renal system and hemochromatosis. Special attention has been directed to them.

The chapters on hyperinsulinism are added because of the importance of knowledge of insulin collapse in the management of diabetic patients receiving insulin and also because of personal interest in spontaneous hypoglycemia attributable to functioning tumors of the islands of Langerhans.

For what I shall have to write in the pages that follow I alone must accept responsibility, but for the examination of much of the clinical material that forms the basis of whatever conclusions may be drawn I am overwhelmingly indebted to many associates. They cannot all be named, especially the graduate students who have served as assistants and contributed to investigation. Among those of the staff to whom I am indebted most for guidance, or who have been concerned directly with the care of the patients, are Frank Mann and Jesse Bollman of the Division of Experimental Medicine and Surgery, Harold Robertson of the Section on Pathologic Anatomy and Thomas Magath of the Section on Clinical

Pathology, Walter Boothby of the Section on Metabolic Investigation, Arnold Osterberg and Marschelle Power of the Division of Biochemistry, Starr Judd, Melvin Henderson, Henry Meyerding and Waltman Walters of the Division of Surgery, Henry Wagener of the Section on Ophthalmology, Henry Woltman of the Section on Neurology, Lawrence Randall of the Section on Obstetrics, and those members of the Division of Medicine who have been my associates in providing for the special therapeutic requirements of patients with disorders of intermediary metabolism. Reginald Fitz, in 1920 and 1921, shared this responsibility, Franklin Adams and Clifford Barborka were with me from 1922 to 1927, and Frank Allan carried on with me from 1927 to 1929, and alone from 1929 to 1931. Those who since 1931 have been so engaged are Edwin Kepler, Edward Rynearson and more recently Randall Sprague.

To the dietitians and nurses who have labored in behalf of this group of patients I also wish to acknowledge appreciation. Foremost among them at present are Miss Mary Foley, Assistant Professor in The Mayo Foundation, and Sister Mary Victor, M. S., Dietitian in Chief, St. Mary's Hospital

To the editorial staff of the Division of Publications of The Mayo Clinic, and to my secretary, Mrs. Hazel Hokanson, I also am most grateful for alert and helpful assistance.

To my publishers I am indebted for much consideration, and especially for their forbearance in the matter of an unusual number of footnotes. The liberal use of footnotes as a method of documentation, a regular practice in books on history or economics, has not been customary in medical writing. This seems to me unfortunate, since footnotes provide a means of supplying valuable contributory material without interfering with the logical development of the thesis By using footnotes freely the hurried practitioner and the beginning student can be saved reading time without sacrifice of more complete exposition.

Several of the chapters in this book reproduce clinical lectures given to various audiences and previously published. For permission to reproduce them I am indebted to the respective publishers of International Clinics, Minnesota Medicine and Medical Clinics of North America. The chapter on "Diabetic surgery"

appeared in a less completely developed form in Christopher's "Textbook of surgery," W. B. Saunders Company. Much other material represents an amplified version of my contribution to Barr's "System of applied therapy," Dr. Barr and his publishers, Williams and Wilkins, having kindly consented to its incorporation here.

RUSSELL M. WILDER.

ROCHESTER, MINNESOTA

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Clinical Diabetes Mellitus and Hyperinsulinism

CHAPTER I

THE SUGAR OF THE BLOOD

The sugar of the blood is dextrose. The amount of it in the water of the blood,[1] namely the concentration or level of the blood sugar, deviates within limits but is characterized normally by remarkable constancy. Gross deviation is prevented by a system of opposing forces, chiefly hormones and nerve impulses and some independent action of the liver. By this means the rate at which dextrose enters the blood is balanced nicely against the rate of its withdrawal, tissue demand for dextrose is met as it arises, plethora is prevented when food is eaten and scarcity is avoided during periods of fasting The expedience of such an arrangement is apparent. Blood sugar in excess of the level at which dextrose is excreted by the kidneys would be wasteful, to say the least, whereas scarcity of sugar is as badly borne by certain tissues as want of oxygen.

THE RANGE OF THE BLOOD SUGAR

The reducing power of the blood of normal men and women after a night's fast, determined by the analytical method of Folin and Wu, represents that of a solution of 0 090 ± 0 030 gm. of dextrose in 100 c.c. of water. Not all of this is due to dextrose. With analytical methods which determine only dextrose, values are obtained which are smaller by from 0 010 to 0 030 gm. per 100 c c than those obtained by the method of Folin and Wu A variable difference in the value for sugar exists between blood drawn from capillaries (arterial blood) and that drawn simul-

[1] Dextrose was found by Power and Peterson to be distributed between the plasma and the corpuscles of the blood in proportion to the water of the plasma and the corpuscles

taneously from a vein. The difference is influenced by factors such as the rate of blood flow, the potency of arteriovenous shunts as described by Grant, and Clark and Clark, and by the rate of utilization of sugar by the tissue. The difference at best is a rough and unreliable index of utilization of sugar by tissues.

EFFECT OF ABSORPTION OF FOOD

As dextrose is absorbed from the bowel during the digestion of a mixed meal, the level of the blood sugar rises, and if dextrose alone is fed in a dose of from 50 gm. or more, as is customary in a dextrose tolerance test, the rise may represent from 0.050 to 0.070 gm per 100 c c. The high point in such a test is normally reached in from thirty to sixty minutes and rarely exceeds 0.160 gm. per 100 c c. The values then fall, and usually they are down to between 0.100 and 0.120 gm. per 100 c.c within two hours. They often continue to fall below the initial value, then rise again to settle finally on the base line, after one or two minor swings up and down. The initial rise of the blood sugar level in such blood sugar time curves is referred to as the "hyperglycemia phase"; the subsequent fall below the base line is spoken of as the "hypoglycemia phase." Great individual variations are encountered in the behavior of blood sugar time curves, even with perfectly normal subjects or with the same subject examined on different days Previous diets have a marked influence, but so do many other factors.

The effect of ingested starch on the level of the blood sugar is less marked than that of a comparable amount of dextrose for the reason that time is required for digestion of starch, so that the rate of absorption of the dextrose derived from it is slower than the rate of absorption of dextrose after dextrose has been ingested.

The effect of ingestion of protein is minimal, even though approximately 50 per cent of protein ultimately behaves in metab olism like dextrose. Protein not only must be digested before its constituent amino-acids can be absorbed, but subsequently these must be acted on chemically by the liver before dextrose is derived from them

The effect of ingestion of fat on the level of the blood sugar is negligible. Absorption of fat is slow, and although the glycerol in it is convertible to dextrose, this represents only about 10 per

cent of the weight of the fat and the amount is too small to influence the blood sugar [2]

STABILITY OR HOMEOSTASIS OF THE BLOOD SUGAR LEVEL

It was stated that the concentration of the blood sugar is maintained within a restricted range by opposing forces and depends on the balance of the activities of various hormones and nerves. The forces seem to be exerted both on the liver and the tissues so that when dextrose is presented to the system the rate of its oxidation is stepped up and simultaneously, as was demonstrated beautifully by experiments of Soskin, Essex, Herrick and Mann, the secretion of sugar by the liver stops and retention of sugar as hepatic glycogen begins. The rate at which sugar must enter the blood to displace this buffered equilibrium is high. In collaboration with Sansum and Woodyatt it was demonstrated that normal men and women, as well as normal dogs, could be given intravenously 0 80 gm of dextrose per kilogram of body weight per hour without provoking glycosuria if the rate of injection was made constant by the use of the continuous injection apparatus devised by Woodyatt and co-workers. Much later Jordan, in work done under my direction, showed with dogs that when dextrose was injected intravenously at a lower rate (0.7 gm. per kilogram per hour), it later, after two hours, could be given at a rate up to 1.5 gm per kilogram per hour, and to one animal at a rate of 2.25 gm, without causing glycosuria. The blood sugar level remained below 0 170 gm per 100 c.c. for the entire time of these injections—from six to eight hours The observations of Jordan were susceptible to the explanation given for the so-called Staub-Traugott effect. Staub, and, independently, Traugott, but before them, Hamman and Hirschman, showed that a second dose of dextrose given by mouth to a normal human subject, an hour or so after a primary dose, has little if any elevating effect on the level of the blood sugar The observations indicate that dextrose when presented to the tissues stimulates the mechanism for its utilization and it has been assumed that

[2] Statements contrary to this have been made by some writers The literature on the subject has been reviewed by Wishnofsky, Kane and Spitz, who gave olive oil alone or olive oil and dextrose to diabetic patients and normal persons and observed that the oil had no elevating effect on the values for blood sugar

the stimulation depends in part at least on mobilization of insulin. The same explanation has been offered for the hypoglycemic phase of the blood sugar time curve when only one dose of dextrose has been given, as in a tolerance test.[3]

The mechanisms for buffering the level of the blood sugar are equally effective against depressions of the blood sugar level, so that prolonged periods of starvation normally can be endured without the development of pathologic hypoglycemia. The effect of undernutrition and starvation on carbohydrate metabolism has been reviewed exhaustively by Chambers. The blood sugar level is lowered very little by fasting, and in dogs, as was shown by Morgulis and Edwards, it may be raised in the later stages when the metabolism of protein increases. The glycogen content of the liver and muscle suffers severely, although complete exhaustion of the glycogen reserves, as Lusk emphasized, is accomplished experimentally only with the greatest difficulty.

Similarly, a diet containing only a few grams of carbohydrate, like the ketogenic diet which I introduced several years ago for the treatment of epilepsy, causes no significant disturbances in the blood sugar level. However, a diet low in carbohydrate, as Adlersberg and Porges, and Sweeney have shown, upsets the mechanism for buffering the blood sugar in such a way that rich feeding of carbohydrate immediately afterward produces greater hyperglycemia than normal. This effect of a low intake of carbohydrate is transient. A few days of a diet richer in carbohydrate restores the normal stability of the system. The phenomenon is of theoretic interest but of less practical significance, it seems to me, than

[3] This view was combated by Soskin, Allweiss and Cohn, who found that when the blood sugar of depancreatized dogs was maintained at a normal level by the simultaneous intravenous injection of dextrose and insulin, giving extra dextrose resulted in a blood sugar level that first rose and then declined below the base line, as is observed in the hypoglycemic phase of the blood sugar time curve of a tolerance test. Under the conditions of their experiment extra insulin to provide for the extra dextrose was not available—the pancreas being out—and since it was not required the authors maintained that the homeostasis of the blood sugar normally does not depend on the ability of the pancreas to secrete extra insulin to provide for ingested or injected dextrose. Ricketts, however, challenged their conclusions with experiments showing that an unchanging insulin effect, such as that provided by daily doses of protamine insulin, in cases of severe diabetes or in depancreatized dogs, will not prevent a hyperglycemic response to ingestion of dextrose. *He did not deny to the liver an independent part in the regulation of the blood sugar*, but believed that its proper functioning under normal circumstances depends on the availability of an extra supply of insulin to meet extra requirements presented by ingestion of carbohydrate

has been supposed by Adlersberg and Porges, and Himsworth. Its explanation is complex. With less sugar presented, the islands of Langerhans are subjected to less stimulation. They undergo some degree of temporary functional impairment and are less ready to meet later demands for more insulin. There is evidence also that sensitivity to insulin is diminished, and Marks suggested that this depends on stimulation, by absence of carbohydrate, of the anterior lobe of the pituitary body with resulting antagonism to insulin activity.[4] Also as a result of studies of Soskin and others there is reason to think that the glycogenic function of the liver is independently disturbed by carbohydrate starvation. Whatever the answer, the effect, as I stated, is transient A permanent derangement of the system cannot be produced by restriction of carbohydrate.

Effect of exercise and other agencies on blood sugar—With physical exertion the demand of the muscles for fuel is met in part by dextrose from the blood, and unless the loss is made good, hypoglycemia ensues The liver readily effects the necessary compensation if the amount of exertion is moderate, but severe exertion, as was found by Levine, Gordon and Derick, will provoke a severe hypoglycemia in healthy men. The signal to the liver that more dextrose is required during exercise is supposed to be given by the lowered level of blood sugar. However, experiments like the one performed by Brosamlen and Sterkel indicate that some other method of signaling may also be involved. Brosamlen and Sterkel found that the blood sugar values of normal fasting subjects fell slightly from a level of 0.080 to one of 0.070 gm. per 100 c.c. after fatiguing muscular work, but when a fasting diabetic patient was subjected to similar work a rise in the value was observed, which the authors attributed to glycogenolysis without oxidation of the sugar produced

[4] Marks commented on resemblances between effects of injection of extracts of hypophysis and those observed when the diets of normal subjects and diabetic patients contain limited amounts of carbohydrate, and he suggested that the hypophysis is concerned in the production of carbohydrate from protein (or fat, or both) and that the greatest demand is made on it when the organism, because of lack of carbohydrate, is forced to obtain its necessary dextrose from protein (or fat) Thus, he thought, when the diet is poor in carbohydrate the hypophysis is stimulated and the peripheral response to insulin is inhibited, and, vice versa, when the diet is rich in carbohydrate the hypophysis becomes less active, the peripheral response to insulin is no longer inhibited and at the same time dextrose is no longer easily mobilized by the liver

A low environmental temperature with or without shivering increases the amount of sugar in the blood. This, to judge from experiments of Cannon and his associates, can be explained by liberation of adrenalin and consequent mobilization of hepatic glycogen. Fright is elevating and causes psychic hyperglycemia. Cannon and his co-workers considered that mobilization of adrenalin, which mobilizes hepatic glycogen, was involved in this.[5] Asphyxia also is elevating; so is fever. Lactation is depressing Irradiation with ultraviolet rays is said to be elevating, roentgen radiation is said to be depressing, and so on through a long list of physical and chemical agencies. To recount them all is unnecessary—what I wish to emphasize is that the mechanism for stabilizing the level of the blood sugar is effective in normal men to such a degree that the deviations up or down by physiologic processes usually are held within bounds and always are promptly corrected.

THE LIVER IN THE HOMEOSTASIS OF THE BLOOD SUGAR LEVEL

We now must consider separately the individual parts of the mechanism which sustain the blood sugar within the relatively minor limits of variation encountered normally. The focal point in the system is the liver. After hepatectomy in dogs or after extensive destruction of the liver of man, by such diseases or poisons as cause diffuse lesions of its parenchyma, no other part of the regulatory system is able to prevent the development of extreme hypoglycemia. The destruction of the liver, however, must be extensive. If as little as 20 per cent of the organ is left intact, abnormality of the level of the blood sugar is not observed. The

[5] The observation of Folin and associates of emotional glycosuria in twelve of seventy students tested before college examinations is widely known. Lusk cited other examples and then added the following comment "Evidently such conditions as these are not to be classed with diabetes mellitus, where there is a fundamental disturbance in the sugar-burning power in the organism It would be of service to distinguish between glycosurias where the *sugar-holding* capacity of the organs has been diminished or overstrained, and the glycosuria of *diabetes* in which the *sugar-burning* capacity has been affected For example, Kleiner and Melzer injected intravenously 4 grams of glucose per kilogram of animal into both normal and depancreatized dogs. The blood sugar rose greatly in both groups of animals, but in the normal animals there was a rapid readjustment through elimination by the kidney, glycogen retention, and oxidation of glucose, whereas in the depancreatized animals, though removal of the glucose by the kidney was active, the other two functions were in abeyance and the blood sugar continued at a high level long after it had readjusted itself in the normal animals"

signs and symptoms of hypoglycemia will be considered later; their first adequate description by Mann and Magath (1921) from observations of hepatectomized dogs, enabled Banting and Best to recognize that the effects of large doses of insulin were due to low blood sugar levels and thus to avoid the mistakes that had been made by earlier investigators who attributed such symptoms to toxic material contained in extracts from the pancreas.

The hepatectomized dogs of Mann and Magath (1921) died in convulsions within a few hours, but if, during any stage of the development of the syndrome, dextrose was injected, the animal immediately and completely recovered.* Also it was found that if continuous injection of dextrose was maintained, or if this sugar was given by mouth at hourly intervals, the hepatectomized dogs could be kept alive for many more hours—from eighteen to thirty-six—in which case they ultimately died from results of hepatic failure other than hypoglycemia.

The amount of dextrose necessary to prolong the lives of hepatectomized dogs was found to approximate 250 mg. per kilogram per hour (Mann and Magath, 1922). Why so much is necessary remains inexplicable. From later experiments of Soskin, Mann and others, it appears that no such export is obtained from the intact liver. In these experiments, also performed on dogs, the flow of blood through the liver was measured by means of thermo-stromuhrs and thus the total amount of sugar entering and leaving the liver could be determined. Data were obtained in periods of fasting and in other periods after injection of dextrose. As I interpret them they indicate that when dextrose was injected sugar was retained by the liver at a maximal rate of 85.5 mg. per minute in one experiment, and that in the fasting periods it was exported by the liver at an average rate of 18 mg. per minute. The weight of the animal was 18.9 kg. Therefore this rate of export would represent only 57 mg. per hour per kilogram of the dog's weight.

*The prompt recovery of these almost moribund hepatectomized dogs, following administration of dextrose, provides a dramatic demonstration of the significance of blood dextrose for the maintenance of life. Such animals also can be restored by injection of other saccharides. Mannose and maltose are almost as effective as dextrose, fructose and galactose are much less so, whereas sucrose, lactose and pentose are useless. Best and Taylor proposed that the action of sugars other than dextrose depends either on their conversion to dextrose by the tissues or on the possibility that they are burned directly in place of dextrose.

The work of Mann and his associates revealed that the glycogen of muscle was not available for the maintenance of the blood sugar in the hepatectomized animal. However, as was shown by Cori, in the presence of the liver, muscle glycogen is used for this purpose indirectly. The glycogen of the muscle, unlike that of the liver, is not hydrolized to dextrose in the body. Its degradation product is lactic acid. However, any part of this lactic acid which enters the blood reaches the liver and there is converted to hepatic glycogen. Thus indirectly, if the liver is intact, muscle glycogen may serve as a supply of sugar for the blood.

The capacity of the liver for removing dextrose from the blood, when dextrose enters the blood stream at a rate too rapid for its immediate utilization by the tissues, is illustrated by experiments reported by Pollock, Millet, Bollman and Wilder, Jr. Dextrose in solution was injected by vein at the constant rate of 2 gm per kilogram per hour into normal and hepatectomized dogs. In the normal animals the excretion of sugar varied from traces in the first hour of injection to a maximum of 0.15 gm. per kilogram of dog weight per hour in subsequent hours, and the level of the blood sugar never exceeded 0.20 per cent. In the liverless animals injected at the same rate, the urine contained from a minimum of 0.8 gm. of sugar per kilogram of dog weight per hour to as much as 1.6 gm. per kilogram per hour and the level of the blood sugar rapidly rose to 0.40 or 0.50 gm. per 100 c.c.

THE PANCREAS IN THE HOMEOSTASIS OF BLOOD SUGAR LEVEL

In the absence of the pancreas, provided hormonal activity which normally is opposed to insulin is maintained, the blood sugar rises to diabetic levels and stays there, even when the organism is fasted; contrariwise, as is now well known, an excessive supply of insulin provokes as severe a lowering of the blood sugar as that which Mann and Magath observed in their liverless dogs.

The evidence that the export of insulin by the pancreas is either stimulated or depressed by nervous control will be considered later. The evidence that the level of the blood sugar directly stimulates the export is undisputed. A small dose of dextrose injected into the artery of a pancreas grafted into the neck

of a depancreatized dog will promptly depress the blood sugar level, whereas the same small amount of dextrose has no such effect if it is injected into the veins and thus is first carried to the liver. Similar results have been obtained with decerebrate cats. The effect represents a chemical control of export of insulin through some action of the dextrose on structures within the pancreas. Thus nervous control is at least not essential (Best and Taylor).

Mechanism of action of insulin.—The action of insulin is believed to be exerted both on the liver and on the tissues of the periphery. As secreted by the pancreas, insulin first passes to the liver, a fact which unquestionably is significant. Its action there is to stabilize the hepatic glycogen by inhibiting the reaction glycogen → dextrose. Also it exerts a sparing action on the catabolism of protein so that neoglucogenesis from protein is retarded.[1] The evidence that a hypothetic formation of sugar from fat also is inhibited by insulin is to my mind unsatisfactory, although this opinion is held by a number of investigators. The increase of glycogen in the liver and muscle of diabetic animals, together with the carbohydrate accounted for by oxidation, seems to account for all the sugar that disappears from the blood when insulin is injected.

The conclusion that insulin acts on tissues other than the liver is based chiefly on the following observations: In the absence of insulin, both in depancreatized dogs and in cases of severe clinical diabetes, the respiratory quotient of animals fed carbohydrate falls to a level comparable to that observed when a nondiabetic animal is either fasted or deprived of any food containing carbohydrate. This quotient (CO_2/O_2) corrected so as to exclude the influence of protein in the diet (the nonprotein respiratory quotient) is that of burning fat (0.70). In the completely

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diabetic state the nonprotein respiratory quotient is uninfluenced by feeding carbohydrate or injecting dextrose, whereas giving insulin promptly changes this condition so that normal, that is, elevated respiratory quotients, are obtained by giving carbohydrate. The respiratory quotient of normal men or animals rises more after administration of insulin and dextrose than it does after the administration of dextrose alone; also when insulin is given with carbohydrate more glycogen accumulates in the muscles. A curious observation, for some time unexplained, is that large single doses of insulin increase the glycogen stores of the liver of diabetic animals but do not do so in normal animals It now appears that an excess of insulin stimulates activity on the part of endocrine glands with an opposing effect, especially the adrenal medulla, with a net result which may represent actual diminution of hepatic glycogen If insulin is administered slowly, and at the same time a liberal intake of carbohydrate is provided, larger amounts of glycogen can be made to accumulate in the livers of normal animals than are accumulated after feeding carbohydrate alone.

Other evidence of the peripheral action of insulin is the observations that the rate of fall of the level of the blood sugar after hepatectomy is less (in dogs) if pancreatectomy also is performed and that in such dogs as well as in dogs that only have suffered hepatectomy the rate of fall is accelerated by injections of insulin.

THE NERVOUS SYSTEM IN THE REGULATION OF THE BLOOD SUGAR LEVEL

The evidence that the nervous system plays a part in opposing hyperglycemia, although not fully established, is strongly suggested. Direct action on the liver is possible, both through parasympathetic (vagus) and sympathetic nerves. Also possible is stimulation of pancreatic secretion of insulin through parasympathetic nerves to the pancreas Fibers of the vagus nerve have been traced to the islands of Langerhans where nonmedullated branches have been seen entering the islet cells. After pancreatectomy wallerian degeneration has been traced up the vagus to the hypothalamic region of the brain. Also transfusion of the brain with hyperglycemic blood was shown by the cross circulation experiments of

La Barre to provoke secretion of insulin in animals decapitated except for the preservation of the vagus nerves. However, the interpretation of the results of these observations will be hazardous until they have been fully confirmed.

The evidence that the nervous system both directly and indirectly is capable of opposing hypoglycemia is well established. The direct action is through sympathetic nerves on the liver; the indirect effect is through stimulation of the adrenal medulla and the action on the liver of the liberated epinephrine[8] Under both conditions hepatic glycogen is released and dextrose thus is discharged into the blood. Macleod and Pearce, although granting that nerve impulses passing directly to the liver release hepatic glycogen, considered that the presence of the adrenal glands might be necessary to maintain the integrity of the glycogenic nerve fibers. Glycogenolytic impulses arise not only in the sugar center of Claude Bernard, in the floor of the fourth ventricle, but also in centers of the hypothalamus.

THE ADRENAL MEDULLA IN THE HOMEOSTASIS OF THE BLOOD SUGAR LEVEL

Blum is credited with the discovery, in 1901, that the parenteral administration of epinephrine elevates the level of blood sugar by mobilization of hepatic glycogen. It also mobilizes muscle glycogen, but, whereas hepatic glycogen is converted directly to dextrose, muscle glycogen, as has been said, yields lactic acid which must first reach the liver by way of the blood stream before it can be made into dextrose or glycogen Prolonged injections of very small doses of epinephrine by creating this supply of lactic acid may in the end increase the glycogen content of the liver, but the immediate effect of even small doses is to decrease hepatic glycogen and with large doses given frequently both hepatic and muscle glycogen can be severely depleted

When the level of the blood sugar is quickly lowered from any cause the adrenal medulla releases epinephrine, and by this means the liver is stimulated to make good the deficiency Boothby and I presented evidence revealing this function of the adrenal

[8] It is also possible that a low blood sugar level acting centrally inhibits the secretion of insulin through stimulation of sympathetic nerves to the pancreas Evidence was advanced by Clark that the vagus may inhibit as well as excite the secretion of insulin

medulla, by demonstrating on human subjects that the so-called reaction to an overdose of insulin was accompanied by an abrupt spike-like elevation of the basal metabolic rate, comparable in all ways to that obtained by the parenteral administration of a dose of epinephrine At the same time we called attention to the fact that the early symptoms of an insulin reaction closely resemble those provoked by an injection of epinephrine. Cannon, Houssay and others later established the correctness of this interpretation by showing more directly that epinephrine was liberated when the blood sugar level was lowered abruptly. Abrupt lowering is necessary. If the level falls more slowly, as it does after overdoses of protamine-zinc insulin, the symptoms referable to release of epinephrine are not apparent.

THE ADRENAL CORTEX IN THE HOMEOSTASIS OF THE BLOOD SUGAR LEVEL

The experiments of Long, and Lukens and Dohan revealed that the hormone of the cortex of the adrenal glands played a part *more important than epinephrine in the homeostasis of the* blood sugar. The action of this hormone also is opposed to that of insulin. Large doses of it are said not to provoke hyperglycemia and glycosuria in normal animals, but if the pancreatic reserve of an animal is previously diminished by partial pancreatectomy, severe hyperglycemia and intense glycosuria result from its injection.

That adrenocortical hormone is antagonistic to insulin was well illustrated by the following experiment performed by Sprague A dog, maintained alive with administrations of sodium chloride and sodium citrate after bilateral adrenalectomy and pancreatectomy, received intravenous injections of dextrose at a rate of 1 0 gm. per kilogram of body weight per hour, and insulin was given hourly in the amount necessary to hold the blood sugar at a constant normal level. The injection of dextrose was continued for nine hours and the amount of insulin required for the entire time was only 5 units. A few days later the same experiment was repeated, giving cortin in large doses before, as well as with, the dextrose. Again the injection of dextrose was continued for nine hours, but this time the dose of insulin necessary to prevent hyperglycemia proved to be 40 units. The amount

of insulin required when cortin was administered equaled that used in a control experiment in which the dog, depancreatized but not adrenalectomized, received dextrose at the same rate.

The importance in carbohydrate metabolism of the cortical hormone was further demonstrated by the behavior of the blood sugar in dogs and cats after ablation of the pancreas and both adrenal glands. Such animals, when fasted, have blood sugar values in the low normal range, or even suffer from hypoglycemia. They excrete sugar in the urine only after feedings of carbohydrate or protein, and in this respect resemble animals which have been subjected to the Houssay operation, which will be described later.

It further was found by Long, Fry and Thompson that giving adrenocortical hormone to normal rats diminished the rate of excretion of nitrogen and increased the stores of glycogen in the liver. These effects are not in opposition to but resemble those of insulin. They perhaps are to be explained by overcompensation on the part of the pancreas to an excess of cortical hormone. Exploration of the function of adrenocortical hormone, at this writing, is in an early stage of development with much conflicting evidence and consequent confusion. Britton and his co-workers found that double adrenalectomy caused depletion of glycogen in both the liver and the muscles, and that this condition could not be corrected by giving dextrose with cortical extract. Addison's disease in man regularly produces a state of moderate hypoglycemia associated not only with poor reserves of glycogen in the liver, but also with asthenia which may depend on a defective supply of muscle glycogen. On the other hand, asthenia confusingly is also a characteristic clinical feature of hyperfunctioning tumors and states of hyperplasia of the adrenal cortex.

THE THYROID GLAND IN THE HOMEOSTASIS OF THE BLOOD SUGAR LEVEL

The action of the hormone of the thyroid gland, like that of the hormone of the adrenal cortex, is opposed in its effect on the level of the blood sugar to that of insulin. It promotes release of dextrose from the liver, causes a loss of muscle glycogen and, of importance in man, although less apparent in experiments on other animals, it shortens the action of insulin possibly by pro-

moting a more rapid destruction of the insulin in circulation. The principal action in physiology of the thyroid hormone is that of a catalyst to oxidation. With the increased metabolism more dextrose is withdrawn from the blood for fuel; however, I have observed that dogs which received injections of dextrose at timed rates actually retained less dextrose when their basal metabolism had been raised by a previous administration of thyroxin than they did otherwise.

Ablation of the thyroid gland is accompanied by a diminished requirement for insulin, and low normal values for blood sugar frequently are encountered in patients who have been subjected to thyroidectomy.

THE PITUITARY BODY IN THE HOMEOSTASIS OF THE BLOOD SUGAR LEVEL

In discussing the pituitary body in connection with the disease diabetes, I shall oppose the theories which attribute to it much of any etiologic or pathogenic significance in diabetes (see Chapter III). However, its importance physiologically in regulating the blood sugar is indisputable. Through its hormones the pituitary is capable of affecting several of the other glands of internal secretion as well as the liver. Of primary importance are the hormones originating in its anterior lobe, although the secretions of its posterior lobe, to a certain extent, also oppose the action of insulin. Evidence presented by Gurd is taken by Best and Taylor to indicate that both the oxytocic and the pressor fractions of pituitrin exert an elevating effect on the blood sugar.

The brilliant work of Houssay and his collaborators on hypophysectomized and depancreatized animals has stimulated enormous interest in the rôle of the anterior lobe of the pituitary body in carbohydrate metabolism. The physiologic literature bearing on this subject, complex in extreme at this writing, has been summarized by Russell, of the Institute of Experimental Biology of the University of California. The following are her conclusions:

"1. Hypophysectomized animals are remarkably hypersensitive to insulin and may show diminished responses to epinephrine. . . .

"2. The removal of the hypophysis alters markedly the response of the animal to pancreatectomy, apparently ameliorating the effects of this operation . . .

"3. Anterior lobe extracts may affect the carbohydrate metabolism of normal, depancreatized or depancreatized-hypophysectomized animals in a manner which is outwardly 'contra-insular' or 'diabetogenic.' This action cannot be considered simply in this light, however, for not all of the effects are similar to those of pancreatectomy and the mechanism of their action is unknown. . . .

"4 Hypophysectomized animals when in good condition and well fed exhibit no marked abnormalities in their carbohydrate metabolism except those noted above, but they suffer an impairment in the normal mechanism by which blood sugar levels are maintained and, apparently, by which the tissue carbohydrate reserves are preserved, in conditions in which the carbohydrate supply is interrupted (as in fasting, phlorhizin poisoning, etc.)

"In the rat, the abnormal rate of depletion of carbohydrate reserves during fasting is accompanied by an apparent increase in the rate of carbohydrate oxidation Both of these effects can be prevented by anterior lobe therapy

"Two principal theories have been advanced in explanation of these and related findings—one, that the anterior lobe controls gluconeogenesis from endogenous protein, if not from fat, administration of its extract causing an increase in available glucose and its removal curtailing the supply, the other theory, that the anterior lobe influences carbohydrate oxidation itself, its presence preventing carbohydrate loss below certain levels and its absence characterized by lack of restraint on carbohydrate oxidation under conditions when such would ordinarily occur."

To me it appears that the theories recounted by Russell are not mutually antagonistic, and that probably the anterior lobe both stimulates hepatic neoglucogenesis and inhibits peripheral oxidation of sugar, with resulting elevation of the blood sugar and antagonism to insulin. Unsettled is the question whether the action of the pituitary hormones in whole or in part is exerted directly on the liver and other tissue, or indirectly through stimulation of the adrenal cortex Or similarly, whether the ameliorating effect on diabetes of hypophysectomy is due directly to removal of the pituitary secretion or indirectly to secondary atrophy of the adrenal cortex. Atrophy of the thyroid after hypophysectomy and the lowered basal metabolic rate of hypopituitarism also must influence the Houssay phenomenon. The clinical evidence pro-

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CHAPTER II

DIABETES MELLITUS: DEFINITION AND DIAGNOSIS

Those who adhere to the unitarian conception of diabetes, as I do, define this disease as an abnormality of metabolism created by insufficiency of the insular activity of the pancreas. In diabetes the homeostasis of the blood sugar level is permanently disturbed. In cases of severe diabetes in which no treatment is employed, abnormal elevation of the blood sugar level is a constant phenomenon. In cases in which the disease is of mildest intensity, abnormal elevation regularly is provoked by administering dextrose. In this characteristic, which, as I interpret it, represents evidence of irreparable disease, clinical diabetes differs most consistently from all other conditions associated with hyperglycemia. Disorders of other glands of internal secretion or of the liver or of the central nervous system, individually or collectively, are capable of disturbing the level of the blood sugar, but the hyperglycemia or tendency to elevation of the blood sugar level in such conditions is impermanent, whereas that in diabetes is permanent except as it may be controlled by restricting the intake of food or by giving insulin.[1]

Abnormalities other than hyperglycemia exist in diabetic metabolism, but none are as useful for diagnostic purposes. Melituria is not pathognomonic, since sugars other than dextrose are sometimes found in the urine of nondiabetic patients, and in the benign abnormality known as renal glycosuria, a low renal threshold for dextrose permits the excretion of dextrose from blood when the level of the blood sugar is within the normal

[1] Lasting hyperglycemia is encountered in relatively few cases of hyperthyroidism and far less frequently in cases of tumor of the anterior lobe of the pituitary body than has been assumed. The infrequency of such associations may be taken to indicate that the normal pancreas can effect a compensation by increasing its export of insulin Therefore, when a permanent hyperglycemia is encountered in cases of this kind a diagnosis of diabetes (pancreatic) would appear to be justified

range.[2] Azoturia likewise is not distinctive. The term is used to designate excretion of nitrogen in excess of the intake. It is only observed in cases of uncontrolled diabetes of intensity, it also accompanies nondiabetic wasting diseases. Ketone formation and ketonuria are inconstant findings in diabetes and occur in nondiabetic patients who are starved or vomiting.[3] In severe diabetes the respiratory quotient is depressed to a value which represents combustion of little else than fat, and feeding carbohydrate will not affect it. This is evidence of inability or diminished ability to oxidize carbohydrate such as is not found in other diseases provoking hyperglycemia. However, in cases of mild clinical diabetes, abnormality of the respiratory quotient is not apparent and in the terminal stage of severe diabetes, when great inanition has occurred, a respiratory quotient previously depressed may again reach normal values. The symptoms of diabetes, namely, polyuria, polydipsia, polyphagia, loss of weight, pruritus and others, are diagnostically significant, if present, but in cases in which the disease is mild they may be absent. Therefore, the criterion most dependable for the identification of the disease dia-

[2] Dr. Frederick M Allen, whose exhaustive research in experimental diabetes laid much of the foundation of our present understanding of diabetes mellitus, has insisted since 1913 "on the distinction between the disease diabetes, and the symptom glycosuria (or hyperglycemia)." He regarded the distinction "as prerequisite to clear thinking on fundamental diabetic problems . . . Most forms of glycosuria and hyperglycemia are not diabetic"

Hyperglycemia is not invariably associated with glycosuria, as was illustrated by a number of cases reported by Davidson. When not accompanied by glycosuria its diagnostic significance is less assured Occasionally, in renal failure the level of the blood sugar is elevated and in such cases, if other evidence of diabetes is missing, a diagnosis of diabete [illegible]
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intake of carbohydrate may be beneficial, subjectively

[3] If a man who has been starved is fed carbohydrate his urine may contain both dextrose and ketone Some time ago, in a case of renal glycosuria, the threshold for dextrose was found to be so low that as much as 60 gm. of sugar was excreted when the diet contained only 100 gm. of carbohydrate. Under these circumstances not enough glucose remained to insure satisfactory oxidation of fat, and the urine contained ketone, yet this condition was not diabetes That the metabolism of carbohydrate under these circumstances was not abnormal was shown when more carbohydrate was fed. The ketones then disappeared and the patient was well, although he continued to excrete dextrose. The level of the blood sugar in this case never was found to exceed the normal limits, even after large doses of sugar had been given by mouth

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od sugar.[4]

DIAGNOSIS

Joslin's rule to consider any patient who has sugar in the urine
have diabetes mellitus, and to treat him as a diabetic patient
il the contrary is proved, is a safe rule to follow in general
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e before the patient is condemned indefinitely to the disci-
ned regimen required for satisfactory maintenance in true dia-
es. Rigid diets and insulin are badly borne by persons with a
cosuria due to lowered renal threshold or to presence in the
ne of a sugar other than dextrose, and physicians who make a
cialty of diabetes frequently are consulted concerning children,
well as by adult patients, whose lives have been made miserable
treatment which they did not need The number of these
stakes is not inconsiderable In life insurance examinations of
ducing urine from 1000 persons, men and women, Exton found
at whereas *dextrose* caused 97 per cent of the 200 reductions
which the value if expressed as *dextrose* exceeded 1 per cent,
caused only 60 per cent of the 800 reductions in which the value
is 1 per cent or less. Furthermore, 10 per cent of the cases in
hich *dextrose* was the reducing substance proved to be cases of
nal or some other form of dextrosuria, not attributable to dia-
tes mellitus. It follows that only about half of the 800 speci-
ens containing 1 per cent or less of reducing substance indicated
e presence of diabetes mellitus. In those cases in which the
duction was not from *dextrose,* in 7.1 per cent glycuronic acid
as responsible, in 2 1 per cent pentose, in 1.8 per cent fructose,
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Hyperglycemia is not invariably associated with glycosuria, as was illustrated by a number of cases reported by Davidson When not accompanied by glycosuria its diagnostic significance is less assured Occasionally, in renal failure the level of the blood sugar is elevated and in such cases, if other evidence of diabetes is missing, a diagnosis of diabetes based on a high fasting blood sugar value may be doubtful In cases like those reported by Davidson, when the absence of glycosuria is not explained by renal insufficiency, I should be inclined to diagnose diabetes mellitus of a very mild degree associated with an abnormally high physiologic threshold for glucose In these circumstances, as Davidson found, a lowered intake of carbohydrate may be beneficial, subjectively.

[3] If a man who has been starved is fed carbohydrate his urine may contain both dextrose and ketone Some time ago, in a case of renal glycosuria, the threshold for dextrose was found to be so low that as much as 60 gm of sugar was excreted when the diet contained only 100 gm. of carbohydrate. Under these circumstances not enough glucose remained to insure satisfactory oxidation of fat, and the urine contained ketone, yet this condition was not diabetes That the metabolism of carbohydrate under these circumstances was not abnormal was shown when more carbohydrate was fed The ketones then disappeared and the patient was well, although he continued to excrete dextrose. The level of the blood sugar in this case never was found to exceed the normal limits, even after large doses of sugar had been given by mouth.

betes is persistence of a tendency to elevation of the level of the blood sugar.[4]

DIAGNOSIS

Joslin's rule to consider any patient who has sugar in the urine to have diabetes mellitus, and to treat him as a diabetic patient until the contrary is proved, is a safe rule to follow in general practice, but I also would urge that proof be obtained in every case before the patient is condemned indefinitely to the disciplined regimen required for satisfactory maintenance in true diabetes Rigid diets and insulin are badly borne by persons with a glycosuria due to lowered renal threshold or to presence in the urine of a sugar other than dextrose, and physicians who make a specialty of diabetes frequently are consulted concerning children, as well as by adult patients, whose lives have been made miserable by treatment which they did not need. The number of these mistakes is not inconsiderable. In life insurance examinations of reducing urine from 1000 persons, men and women, Exton found that whereas *dextrose* caused 97 per cent of the 200 reductions in which the value if expressed as *dextrose* exceeded 1 per cent, it caused only 60 per cent of the 800 reductions in which the value was 1 per cent or less. Furthermore, 10 per cent of the cases in which *dextrose* was the reducing substance proved to be cases of renal or some other form of dextrosuria, not attributable to diabetes mellitus It follows that only about half of the 800 specimens containing 1 per cent or less of reducing substance indicated the presence of diabetes mellitus. In those cases in which the reduction was not from *dextrose*, in 7.1 per cent glycuronic acid was responsible, in 2.1 per cent pentose, in 1.8 per cent fructose, in 1 6 per cent vitamin C and in 0 6 per cent galactose. Recent employment of vitamin C in a pharmaceutic form suggests that this will be encountered in the future more often than in the past The figures for pentose and fructose bear out the supposition that

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of diabetes is affected, as he said, by the existent degree of activity of the Gegenregulation The severity of the diabetes resulting from insufficiency of the insular organ, and the sensitivity of the patient to injected insulin may be influenced profoundly by the state of activity of other regulators of the blood sugar

pentosuria and fructosuria occur more frequently than is indicated in the literature.

Proof for the diagnosis in doubtful cases also must be demanded for the reason that diabetes mellitus continues to be regarded as cause for rejection of applications for life insurance, and because unfortunately many employers refuse to consider applicants if they are diabetic. The proof required ordinarily is obtained with no great difficulty. The cardinal symptoms of diabetes, always evident in cases of severe untreated diabetes—polyuria, polydipsia, polyphagia and loss of weight despite a large intake of food—are pathognomonic, while the presence of reducing substance in the urine is always suggestive and when found immediately prompts further investigation. The value for sugar in blood drawn before breakfast usually will be diagnostic if it is as high, or higher, than 0.12 gm. per 100 c.c., provided always that no other cause for hyperglycemia is apparent. However, low fasting values for blood sugar may be obtained in true diabetes and care must be taken not to be misled by this. In some cases in which children are seen during the remission which often follows the original more or less stormy development of diabetes in childhood, and in many cases in which the patients are children or adults and the diet has been restricted, or in cases in which insulin has been taken by malingerers, low fasting values for blood sugar may be obtained. Under these circumstances a test for tolerance to sugar is called for. The blood sugar time curve of the standard dextrose tolerance test usually is diagnostic of diabetes mellitus, but its evaluation must be made with due attention to the previous diet and to the presence of infection or other complicating conditions, particularly those such as hyperthyroidism, in which endocrine organs normally engaged in maintaining the homeostasis of the blood sugar are diseased.

Dextrose tolerance tests.—The dextrose tolerance test, the one dose-three hour test, as usually performed, is made by giving dextrose by mouth. In The Mayo Clinic, 1 gm. of dextrose is given for each kilogram of the patient's body weight. It is dissolved in water to make a 20 per cent solution and flavored with lemon juice. The patient must have had no breakfast and must not have been restricted in his diet, particularly in carbohydrate, for three or four days before the test is made. The blood and urine are

examined for dextrose at the zero hour and at spaced intervals after the patient begins to drink the solution. The peak of the increase in the concentration of blood sugar usually is recorded by the determination made at thirty minutes. The normal value for the sugar in the venous blood at this time ought not to exceed 0 180 gm per 100 c c and between the second and third hours the value should have returned to the fasting level (Fig. 1). Frequently the curve then swings below the fasting level. The curve in diabetes reaches its peak later and remains above the fasting level more than three hours (Fig 2).

Experience with Exton's simplified tolerance test, the two dose-one hour test, has been favorable and this now has become

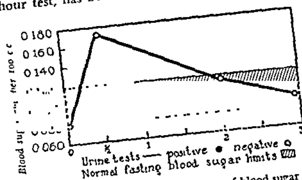


Fig 1 —Normal tolerance The concentration of blood sugar was normal before the test, it rose to a peak value of 0 170 gm. per 100 c c. in one half hour after the test was begun but returned to normal limits in two hours None of the specimens of urine contained sugar

a routine procedure at the clinic. In the Exton test, 50 gm. of dextrose in a 20 per cent aqueous solution is given twice—at the zero hour and exactly thirty minutes after the patient has started to drink the first dose Venous blood is collected just before the first dose is given and exactly one hour after the patient started to drink the first dose of the solution. Exton also advised withdrawing blood at the half hour, but Matthews, Magath and Berkson, in a review of accumulated data, found that the most significant criterion in this test is the value for the sugar of the blood taken at the hour. If this value is less than 0 160 gm. per 100 c c. the case is not one of diabetes mellitus. If it is more than 0.180 gm per 100 c.c, the therapeutic diagnosis is diabetes mellitus Equiv-

ocal results occasionally are obtained by any method and, when values between 0.160 and 0.180 are obtained, or if for any other reason the interpretation is doubtful, *even after repeating the examination*, the diagnosis should be "diabetes suspected" and the patient advised accordingly. He then ought to test his urine at least once a week, avoid the use of sugar and sweets or large single meals of any kind, avoid overweight and consult a physician if glycosuria persists or recurs despite these precautions.

Dextrose tolerance tests give very imperfect information about the severity of diabetes. They should be resorted to only as an

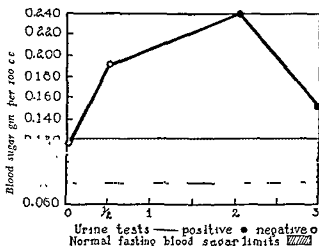


Fig 2—Diabetes mellitus. The concentration of blood sugar was within normal limits before the test and within the limits of normal alimentary rise at the determination made one-half hour after the test was begun. It failed, however, to return to normal limits by the third hour.

aid in the diagnosis in cases in which it is questionable. With mild diabetes, which alone offers diagnostic difficulty, the amount of sugar given in the test can do no harm, in cases of severe diabetes it may be injurious. Allen's partially depancreatized dogs, gaining tolerance and progressing toward complete recovery on starch diets, could be "sent into hopeless diabetes by admixture of glucose."

Negative reactions to tolerance tests almost always can be accepted with assurance as evidence of absence of diabetes, although one might be led astray by a case of mild, true diabetes in which the patient has severe diarrhea or other gastro-intestinal

disturbance interfering with absorption of the dose of dextrose. Also in hypothyroidism, hypopituitarism and Addison's disease, a very mild coexisting diabetes could be obscured. Positive responses to the test, by patients with diseases or abnormalities other than diabetes, offer the principal difficulty. Infection and hyperthyroidism may elevate the concentration of fasting blood sugar and provoke a diabetic-like response. The same may or may not occur with any one of the following conditions: hyperpituitarism (acromegaly, pituitary basophilism), adrenal tumor, hypertension, arteriosclerotic nephritis, hepatitis,[5] cancer, pregnancy, severe anemia, coronary thrombosis (see p 343), arthritis, gout, osteitis deformans, encephalitis and muscular dystrophy. In addition, if a diabetic type of response is to be interpreted correctly, the patient must not recently have engaged in unusual exercise or have taken alcohol or any drug, nor must he have been subject to starvation, particularly carbohydrate starvation nor to any recent emotional disturbance or physical injury.

In other words, tests for dextrose tolerance, if they are to give reliable results, must only be made under strictly basal (standard) conditions, and when any disease is present other than the suspected diabetes, whatever response is obtained must be interpreted with caution. In the presence of another disease a diagnosis based exclusively on a positive response to a dextrose tolerance test can be no more positive than "diabetes suspected," but in that case other examinations should be made later and the patient should remain under the supervision of his physician until the suspicion is removed. True diabetes is persisting, so that in time a decision almost always can be reached, either on the basis of subsequent tests or by the development of conspicuous symptoms. A diabetic-like response to the tolerance test is conclusive evidence of the presence of diabetes only in the absence of any other cause for disturbed carbohydrate metabolism.

[5] Coller and Troost have pointed out that hepatic damage is likely to provo[ke] a low value for the fasting blood sugar, but that it may produce a diabetic ty[pe] of response to a dextrose tolerance test. The hypoglycemia phase of the respo[nse] to such a test frequently is exaggerated. Coller and Jackson emphasized that t[he] response is not necessarily the result of injury to the pancreas, but may be cau[sed] simply by disturbance of the glycogenic function of the liver. Studies with [a] respiration chamber in two cases of disease of the gallbladder "showed that ca[rbo]hydrate was oxidized normally." The patients in these cases and in a third had symptoms related to episodes of hypoglycemia which were modified b[y re]moving the gallbladder.

NONDIABETIC MELITURIAS

I have mentioned (see p 21) the considerable incidence of nondiabetic reducing urines in cases in which persons are examined for life insurance. Whenever the test of urine for reducing substance gives positive results, it is my practice to determine the level of the blood sugar before breakfast. If this is high (more than 0.12 gm. per 100 c.c.) the therapeutic diagnosis is diabetes mellitus—if it is low, a test for dextrose tolerance is obtained. If the response to the tolerance test is nondiabetic, the nature of the reducing substance in the urine is determined, and under these circumstances if the reducing substance is dextrose, renal glycosuria is diagnosed, at least presumptively. Or in these circumstances if the reducing substance is not dextrose, the several other sugars that may be responsible for the reducing urine are tested for.

Pentosuria (*Xylosuria*).—Pentosuria occurs infrequently. Lasker and her collaborators, reviewing the literature, found only 170 recorded cases of pentosuria. In 119 of these cases the patients were males and in fifty-one they were females. In every case the patient was a Jew. The pentose in these cases was l-xylose, also called l-xyloketose, although in many earlier reports on pentosuria the sugar, perhaps incorrectly, was called arabinose. Pentosuria seems to be an inborn error of metabolism, inherited as a recessive characteristic It occurs with considerable frequency in affected families and has been reported in twins by Enkelwitz and Lasker. Patients with pentosuria are often of a neurasthenic type and complain frequently of headaches, otherwise, no symptoms are evident. The prognosis is entirely favorable, and no treatment is indicated

Lasker and Enkelwitz have described a simple method for the detection and quantitative estimation of l-xylose in urine. The Bial test for pentose also may be used. Xylose is dextrorotatory, but is not fermented by yeast. Like other sugars it gives a characteristic osazone with phenylhydrazine. Experiments by Larson and his collaborators showed that feeding synthetic d-xylose to rats caused the deposition of glycogen in the liver; it is considered possible that persons with pentosuria lack the ability to metabolize this sugar.

Fructosuria.—This anomaly is also thought to be an inborn

error of metabolism. The number of cases reported is small, although Silver and Reiner, in 1934, from one hospital were able to add six new cases to the twenty-seven then in the literature. Undoubtedly the condition is more common than is suggested by the limited references to it. In four of the cases reported by Silver and Reiner the patients were brothers, two in one family, two in another. Fructosuria is symptomless; the diagnosis depends on examination of the urine and blood Fructose reduces Benedict's qualitative copper reagent without heating The test for it, proposed by Lasker and Enkelwitz, is based on this property. Roe has adapted the old Selivanoff test so that it gives reliable quantitative results for fructose in blood and urine. The blood of normal persons, even after the ingestion of meals containing fructose, contains, at most, mere traces of fructose, while that of persons with fructosuria will show considerable quantities. Advantage is taken thereof in a fructose tolerance test used by Silver and Reiner.

Fructosuria is harmless and requires no further attention once the diagnosis has been established, except to warn the patient that his melituria is benign and thus spare him the hardship that unnecessary treatment with insulin may inflict. I well recall a case in which the diagnosis of fructosuria was established by the presence of a normal blood sugar and a positive Selivanoff test on the urine. The patient, who was a man, was using insulin in an attempt to suppress his melituria and was suffering from symptoms of chronic hypoglycemia to such an extent that for several years he had been unable to work He was cured by the advice to stop using insulin

Fructose also has been found with dextrose in the urine of patients with true diabetes mellitus.

Lactosuria.—Lactosuria is considered elsewhere, in connection with the subject of pregnancy and diabetes (see p 234)

Galactosuria—Few reports are available of the finding of galactose in the urine Bansi was cited by Marble as having reported a case of paroxysmal excretion of galactose before and during menstruation, and Mason and Turner, also were cited by Marble, as having reported a case of galactosuria in which the patient was a Negro boy The boy was maldeveloped and malnourished An enlarged liver, an enlarged spleen and albuminuria were found,

normoglycemic glycosuria is benign and demands no treatment.[6] It is a permanent condition consisting essentially of an abnormally low renal threshold for dextrose. The hereditary character of the abnormality has been commented on by a number of writers, among them Hjarne, who in a family of 199 blood relations found that thirty-four members had this condition. The marriage of persons who probably were both subjects of normoglycemic glycosuria produced no "summation" in the direction of diabetes mellitus, and although Hjarne, in the same family, found seven instances of diabetes mellitus, he concluded that the two forms of glycosuria had different origins and that their occurrence in the same family was a chance coincidence

Powelson and I encountered a high familial incidence in a group of eighty-two cases of normoglycemic glycosuria at The Mayo Clinic. Twenty-three of the patients came from families in which other members had glycosuria, also apparently benign The patient in one of these cases, a woman, aged fifty-five years, had six children, all of them living and well. We examined four of the six and in all four obtained reactions characteristic of normoglycemic glycosuria. We obtained a specimen of urine from a fifth and found that it contained sugar My confidence in the innocence of normoglycemic glycosuria dates from the time of this study with Powelson. Not one of the patients in the eighty-two cases previously observed at The Mayo Clinic had later developed diabetes mellitus. Subsequent experience has been equally reassuring Thus far only two patients in several hundred cases in which glycosuria was associated with a perfectly normal response to a tolerance test have returned to the clinic with diabetes mellitus. This proportion of diabetes doubtless occurs in all patients returning to the clinic.

Statements that insulin is without effect in normoglycemic glycosuria are incorrect. The dose of insulin required to depress the concentration of sugar in the blood of any nondiabetic person is large in relation to the dose required to bring to normal the

[6] The only exception to this statement, in my opinion, is encountered in pregnancy (see p. ...) [illegible]

Alimentary hyperglycemia.—Many cases formerly designated alimentary glycosuria were cases of cyclic normoglycemic glycosuria. In addition, however, patients are encountered who respond to the one dose-three hour dextrose tolerance test with a blood sugar time curve that starts at a normal level, goes higher than the normal "ceiling" for the blood sugar one hour later, and yet falls to a normal level by the end of two hours (Fig 5). The condition seems to represent delay in mobilizing the mechanism involved in increasing the rate of utilization of sugar. The hyper-

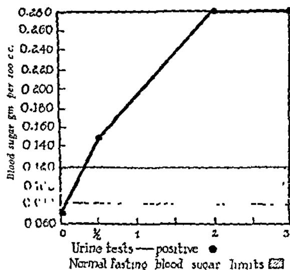


Fig 6—Diabetes innocens The concentration of blood sugar is subnormal before the test, a high peak is reached tardily and the return to normal is delayed as in diabetes mellitus, a low threshold results in continuous glycosuria.

glycemia and glycosuria of nondiabetic patients who have hyperthyroidism frequently are of this type, but other examples also occur. Maclean designated this the "lag type of response." The prognosis is less certainly favorable than with normoglycemic glycosuria.

Diabetes innocens—An extremely rare inexplicable condition is represented by one of the cases in the report by Powelson and me, by a case reported from my service by Parsons, and by a few others in the literature.[7] The renal threshold for dextrose is

[7] The disturbance in these cases probably does not involve the pancreas. It is more likely to depend on some unusual isolated abnormality of the glycogenic

subnormal, and the fasting blood sugar value is normal or subnormal. However, in the one dose-three hour dextrose tolerance test the values rise abnormally and stay high for three hours. The blood sugar time curve is thus indistinguishable from one obtainable in any mild case of diabetes mellitus (Fig. 6). The renal threshold being low, glycosuria is continuous, yet the patient remains well with no treatment. In one of the cases referred to, the thirty-two-year-old patient, a woman who weighed 136 pounds (61.7 kg.), had had glycosuria for thirteen years, that is, since the age of nineteen years. At first she had restricted her diet, but this was only for a short time. When we saw her at the clinic she had been eating without restriction for eight years, excreting dextrose continuously, yet had noted no change in weight and no symptoms of any kind. Our diagnosis of diabetes innocens was based on the duration of the symptomless glycosuria (thirteen years) and on the fact that the patient was young. Untreated diabetes mellitus in young persons almost always is progressive. Our opinion as to the benign character of the condition was justified by the next five years, which passed without any evidence of progression of the condition It should be emphasized that the diagnosis of diabetes innocens can be made with confidence only after many years of observation, and then probably only in cases in which glycosuria has been known to have existed from youth.

Glycosuria of pregnancy.—This condition also is characterized by a low renal threshold for dextrose. It is considered elsewhere (see p 234).

Sapremic glycosuria —The term "sapremic glycosuria" was introduced by Higginson to designate glycosuria that accompanies toxic conditions and various infectious diseases in nondiabetic persons. It is not uncommon to find elevated blood sugar values and reducing substances in the urine of persons with furunculosis, and although this should always arouse the suspicion of diabetes, it frequently happens that the abnormalities disappear completely once the infection is overcome. According to Cammidge, gly-

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function of the liver Evidence of disturbance of any other hepatic function is not obtained The designation "diabetes innocens" is bad, not only because the condition is not true diabetes, but also because the same term formerly was employed improperly to designate the condition now called "normoglycemic" or "renal" glycosuria.

curonic acid, pseudolevulose and pentose occur more commonly than dextrose under such circumstances, and when dextrose is found Cammidge is inclined to regard the patient as, at least, a potential victim of diabetes. This may be the safest attitude to take, at any rate, any such patient should receive the benefit of very careful consideration, and diabetes should not be ruled out unless the results of a later tolerance test indicate a perfectly normal condition.

DIABETES MELLITUS WITH LOW RENAL THRESHOLD

The threshold in diabetes mellitus is usually normal, although in cases of long standing, particularly in those in which diabetes is complicated by arteriosclerosis and advanced age, it may be high (Taussig), and after a long period of treatment with insulin it may rise (Major and Davis). This is true even when the kidney responds normally to the ordinary tests of renal function. Occasionally, but rarely, a low threshold is found. We have observed a number of such cases at the clinic. Sugar may be excreted continuously under these circumstances, even when enough insulin is given to maintain the blood sugar at values well within the normal range, and hence the qualitative tests of urine, on which ordinarily such large dependence is placed as a guide to management, are no longer helpful, and frequent determinations of the concentration of blood sugar must be made in order to gauge the doses of insulin. Or one must make quantitative analyses of twenty-four hour specimens of urine, as Curran and Mills suggested, and consider as "normal" any amount of sugar not greater than that previously determined as the amount excreted when the concentration of blood sugar is within the normal range. The quantity excreted will vary with each case, depending on the height of the threshold. Frank has pointed out that certain cases in which diabetes has been described as refractory to insulin may be cases of this type.

TRAUMATIC DIABETES

The possibility of trauma provoking diabetes is not only of scientific but of medicolegal significance. Excellent reviews of the literature on the subject, together with the report of many

illustrative cases, are contained in papers of Jacobi and Meythaler, and Thomsen.

Injury of the pancreas by direct abdominal trauma is theoretically an exciting or provocative cause of diabetes; the unlikelihood of its resulting in more than a transitory disturbance is supported by the fact that experimental production of diabetes mellitus necessitates the almost complete removal of the pancreas. The deep situation of the pancreas in the upper part of the abdomen makes it improbable that any injury sufficiently severe to cause almost complete disability of the organ would fail to produce fatal results by damage done to neighboring organs.[8] Therefore such a cause of lasting diabetes must be unusual.

Severe febrile infection of long duration, especially septicemia, may so injure a normal pancreas by inflammation or toxicity as to lead to diabetes, but from common experience this is extremely rare. It probably is less unusual for long-continued* sepsis to transform a latent pancreatic insufficiency to one that is evident.

Organic injuries to the central nervous system, according to Jacobi and Meythaler, are neither etiologic nor provocative factors in diabetes. In the series of previously diabetic patients studied by Thomsen, trauma provoked exacerbation in about a half. The exacerbation was independent of the kind and site of the trauma. It set in immediately and had an average duration of twenty-six days. In no case was the exacerbation permanent, and the assertion frequently made that physical trauma is able to exacerbate a latent diabetes so that the disease becomes manifest is considered by Thomsen as incorrect.

Psychic insult of a severe and lasting character does not provoke true diabetes, but may intensify the disease if it pre-exists, or may temporarily bring to light a condition previously inconspicuous. The positiveness with which both traumatic and psychic insult are excluded as causes of diabetes by Jacobi and Meythaler is largely based on the experience of the World War. Joslin is quoted as finding only two instances of diabetes among 40,000 American soldiers at Mesves, France, although urinalysis was made systematically, and in Germany, where in the last years of the war

* Dr H. Gideon Wells, in his lectures on pathology at the University of Chicago, told us that the assassin's bullet fired at McKinley destroyed the pancreas, so that for the few days before the death of the wounded President sugar was excreted in the urine.

older and physically less qualified men were drafted, diabetes was uncommon. Gottstein and Umber, among 4,041 soldiers in Berlin, found the incidence only 1.2 per thousand, whereas among the civilian population of Charlottenburg it was 2.3 per thousand. It is recognized that neurogenic (extra-insular) glycosuria is a common occurrence after both physical and psychic trauma, but this condition is transitory, and that it ever leads to insular deficiency is not established.

Jacobi and Meythaler set up the following criteria for the diagnosis of "traumatic" diabetes:

1. There shall be nothing in the history prior to the accident pointing to either evident or latent diabetes, all previous attending physicians having been interrogated, as well as members of the family and other intimates.
2. The first signs of diabetes, or signs of intensification of any pre-existing diabetes, must follow soon after the trauma; a year is the longest interval permissible.[*]
3. The existence of true diabetes must be established with certainty; demonstration of transient glycosuria is insufficient evidence; demanded are glycosuria and hyperglycemia of long duration and actual intolerance to carbohydrate.

Fracture of bone.—It was stated by Jacobi and Meythaler that recognition of a traumatic origin or of traumatic aggravation of pre-existing diabetes should only rarely be possible. However, in sixty-one cases of fractures observed at the surgical clinic of Kiel, Germany, previously unsuspected diabetes was diagnosed in three by Konjetzny and Weiland, and in our experience at the clinic fracture has led not uncommonly to aggravation of pre-existing diabetes. The following cases were reported by Pollack from The Mayo Clinic. In the third case some question remained as to whether the intense glycosuria could be called a neurogenic (chromaffinic) glycosuria, since insulin was required for forty days after the accident. It is not impossible, as Pollack stated in his comment, that fat embolism of the pancreas or liver accounts for the disturbed metabolism of carbohydrate after fractures, although the consensus seems to be that fat emboli disappear within fourteen days, and the period of upset tolerance is from thirty to

*The application of such a rule would eliminate from consideration any number of men who have successfully laid claim to federal compensation on the basis of service connection of a diabetes which first became evident years after discharge from the army.

forty days. A factor of some importance in prolonging the period may be the enforced inactivity of the patient.

A woman, aged sixty-six years, had been known to have diabetes for five years. She sustained a traumatic fracture of the surgical neck of the humerus and of the right hip. Whereas, previous to the accident her urine had been free of sugar without the administration of insulin, for almost thirty days following the fracture she required 25 to 40 units of insulin daily.

A woman, aged sixty years, had had diabetes for four years. Her diabetes had taken a variable course She sustained an intertrochanteric fracture of the femur at a time when she was taking 70 units of insulin daily. For thirty days following the accident larger doses of insulin were required, and on the fifth day, in spite of the fact that 105 units were given, she excreted 33 gm of dextrose, at that time the diet was liquid and contained less carbohydrate than it did before

A man, aged forty years, was knocked at least 70 feet down a road by an automobile which was traveling at a rate of 60 miles an hour. Multiple fractures of the long bones were found The possibility of an undiagnosed fracture of the base of the skull was not excluded. There was no history of diabetes previous to his admission, yet at the time of the first examination reduction by the urine was graded 4 on a grading basis of 1 to 4 and the value for blood sugar was elevated Treatment with insulin and by diet was instituted In about forty days administration of insulin was discontinued, although a restricted diet was given On the one-hundred and sixth day after his admission a dextrose tolerance test was carried out The curve obtained was practically normal, that is, the value for blood sugar returned to normal at the end of three hours

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CHAPTER III

THE PATHOGENESIS AND PREVENTION OF DIABETES*

Every thoughtful physician is impelled, on occasion, to question whether therapeutic achievement may not interfere dangerously with those natural forces which, unobstructed in the past, have sustained the vigor of the race; whether his efforts to help the weak may not in the end create more weakness and, in sum, whether the ultimate social consequences of his labors will be socially beneficial or otherwise. These inquiries are odious; nevertheless they insistently are forced on our attention by conditions such as diabetes where bioplasmic inferiority is involved. Treatment for diabetes now is so satisfactory that the affected individual can be maintained in normal vigor for a span of years that may equal a normal lifetime. In this we take a natural pride; at the same time we must recognize that the ultimate result of improved treatment of this disease, as of many others, may in the long run be socially deleterious and that social advantage demands prevention more than treatment.

INCIDENCE OF DIABETES

The incidence of diabetic morbidity is unknown, but the indications that it is increasing are very clear. An illustration is our *experience at The Mayo Clinic. Patients come to the clinic* for every ill imaginable, there being no more selection of them than results from the expenses of the necessary travel. In 1920, diabetes was discovered in less than 0 66 per cent of all new cases (primary registrations); in 1936, it was present in nearly 2 per cent. The rate of increase has been much the same from year to year. The statistics are unadjusted; they are influenced, doubtlessly, by the average age of Mayo Clinic patients, which is relatively high, and therefore the figure given of almost 2 per cent should not be interpreted as representing the incidence of morbidity from this

* Read before the New York Diabetes Association, Academy of Medicine, New York City, October 15, 1937 Published also in Medical Clinics of North America, July, 1939

disease in the population at large. The statistics also may be influenced by some selective attraction of patients with diabetes, but what selection has occurred has been the same throughout the period of years considered and, furthermore, the experience of others has been similar.[1] Diabetes was encountered infrequently before 1920; it now has become one of the most common diseases. The change is not accounted for by longer lives, made possible with insulin, because the death rate from diabetes has been increasing concurrently, rising for the United States from 16 per 100,000 in 1920, to 22.2 in 1935.

THE PRIMARY CAUSE OF DIABETES, INADEQUATE INSULAR RESERVE

Knowledge of the etiology of a disease is considered to be a prerequisite to effective prevention. Unfortunately, however, the known facts about diabetes appear to some physicians so contradictory as to preclude a decision regarding pathogenesis, not to speak of etiology. A source of great confusion has been the inconsistency between the lesions found in the pancreas and the degree of severity of diabetes. In some severe cases the islands of Langerhans are normal in size and number and normal in appearance, whereas in some mild cases, and even occasionally in the absence of evident diabetes, the insular tissue is grossly abnormal. To add to the confusion came the indisputable evidence, presented by Houssay and his followers, that the anterior lobe of the hypophysis is involved to a very important degree in the metabolism of carbohydrate, the observation of Long and Lukens that the suprarenal gland is similarly engaged, and that of Soskin and Mirsky that the condition of the liver plays an important part. Some men, clinicians as well as physiologists, have been led by these difficulties to depart from the unitarian theory, by which diabetes was attributed

[1] A house-to-house survey conducted in 1929 by the Massachusetts Department of Public Health, cited by Lombard and Miner, showed 10 per cent of the total population of Massachusetts to be affected with chronic disease, and three per thousand to be affected with diabetes. In other words, 3 per cent of the chronically diseased had diabetes. A census of hospital beds, taken September 1, 1929, showed that 0.72 per cent were occupied by patients admitted for diabetes, and 0.34 per cent were occupied by patients in whom diabetes contributed to the infirmity. The total of hospital patients affected with diabetes thus was 1.06 per cent, a figure which almost exactly equals that for diabetes found among new patients registering that year (1929) in The Mayo Clinic (1.04 per cent).

primarily to disorder of the pancreas, and to locate the original disturbance in some other part of the system of nerves and endocrine checks and balances normally active in holding the level of the blood sugar within accepted bounds.

A fact almost ignored, however, in some of the recent discussions of the subject is that no single feature of diabetic metabolism fails to be entirely corrected when insulin is given in appropriate doses. Another fact that frequently is lost sight of is that total ablation of the pancreas, by experimental means in animals or by disease in man, is the only way in which diabetes *always* can be provoked. A third fact of primary importance is that the normal pancreas possesses an enormous factor of safety.[2]

The three facts together—that diabetes is completely corrected by administering insulin, that diabetes, in normal animals and man, can be provoked only by very complete destruction of the insular mechanism; and that diseases and conditions which precipitate diabetes do so in only a very few of the many cases in which persons are affected by them—these facts, taken jointly, logically admit of only one interpretation; that the normal pancreas possesses the capacity to meet any demands that can be placed on it by overactivity of such antagonists as the pituitary or adrenal, and even can withstand extensive damage to itself without losing its ability to meet ordinary demands. Therefore, when a pancreas fails, unless its insular tissue has been destroyed almost completely, its decompensation must depend primarily on insufficiency of its original capacity to make insulin; in other words, on insufficiency of its insular reserve.[3]

[2] Minkowski, and later Allen, showed that as much as nine-tenths of the pancreas must be removed from dogs before the capacity of the organ is diminished enough to interfere [illegible] the factor of safety [illegible] Long and Lukens [illegible] leads ultimately to [illegible] the deposit of iron, [illegible] parable to total par[illegible] tosis the clinical conditions *destructive to the pancreas produce diabetes infre-* [illegible]

[3] I am using the terms "reserve" and "decompensation" in the same sense [illegible] which they are used in connection with the heart The "cardiac reserve" represents the capacity of the heart to endure strain. Exhaustion of its reserve results in cardiac decompensation, from which complete recovery is a rare occurrence. The pancreatic reserve, or more specifically the insular reserve, represents the endurance

The newer knowledge of the physiology of the pituitary, adrenals and liver, important as this is to an understanding of the regulating of the blood sugar, does not affect these conclusions. The studies of Houssay and those of Long and Lukens have made us more conscious that the pituitary and the adrenals play a part in determining the degree of severity of diabetes, but thus far search in the wards for cases which unequivocably can be ascribed primarily to disease of either of these organs or to the liver has been in vain.[4] Diabetes of the acromegalic differs only in being more variable in intensity; that seen in patients with basophilic tumors of the pituitary or carcinoma of the adrenal cortex usually is benign but otherwise has no unusual features. Furthermore, it is only with the greatest difficulty that lasting diabetes is produced by injecting extracts of the pituitary or adrenal glands into normal animals. Young recently has effected this, but it has been with the use of amounts of hormone that exceed those to be anticipated in pituitary disease. The usual result of injections of smaller amounts of pituitary hormone is to produce, at most, a transitory elevation of the blood sugar.

That the intensity of pre-existing diabetes is influenced by the activity of other parts of the endocrine system has been recognized for many years When a patient, previously diabetic, acquires hyperthyroidism, his diabetes is aggravated; vice versa, if myxedema develops spontaneously, the previous degree of diabetic intensity is greatly diminished Foster, Pemberton and I were able to show that total thyroidectomy, in a case of uncomplicated diabetes, appreciably diminished the intensity of the diabetes The

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of the insular apparatus; the exhaustion of this reserve results in pancreatic or insular decompensation, and as is true in the case of the heart, recovery of normal function after decompensation is rare

[4] Lande and Pollack reported three cases in which direct correlation was found between the degree of glycosuria and that of impairment of hepatic function Insulin in large doses was required in each case to control the excretion of sugar, yet in each case after normal hepatic function had been restored by adequate drainage of the biliary tracts, normal responses to tests for sugar tolerance were obtained Other examples of similar hepatogenous diabetes were cited from the literature, but they are few and certainly represent an unusual occurrence In a case of Himsworth of severe refractory diabetes, necropsy revealed a grossly damaged liver and a normal appearing pancreas The phenomenon may be related to that of resistance to insu-
n in true diabetes, which likewise frequently is associated with extensive lesions
f the liver Observations such as these do not detract from the importance of in-
lin in the maintenance of normal carbohydrate metabolism. They merely show
at the liver must be capable of removing dextrose from the blood stream to pre-
nt glycosuria, when the rate of supply is greater than normally can be tolerat...

observation also has been made by Schnitker and his associates Houssay's hypophysectomized-depancreatized dogs and Long and Lukens' adrenalectomized-depancreatized dogs are other illustrations of the influence of other endocrine glands *on the intensity* of diabetes. Their animals, contrary to statements occasionally made, are not free from diabetes Given sugar to eat they promptly excrete it. When fed abundantly, they develop almost the same degree of glycosuria as dogs or cats that only have been depancreatized.[5]

Therefore, none of this recent evidence affects the question of the primary cause of diabetes mellitus, and it seems to me that we still ought to adhere to the theory of diabetes as it originally was maintained by Naunyn that with very rare exceptions the primary cause is an inborn biologic inferiority, primarily of the insular reserve[6] This thesis in recent years also has been extensively developed by Umber. It is accepted by Woodyatt, by Joslin (1937)—recently with some reservations—and by many other authorities.[7]

[5] Long, in a Harvey Lecture delivered April 15, 1937, summarized the evidence on the question of how pancreatic diabetes is ameliorated by hypophysectomy. It was his conclusion that there is some restoration of the ability of the tissues to *oxidize glucose while, at the same time, the amounts presented to them (by the* liver) are reduced to a level which is within their capacity to dispose of without excessive urinary loss. Quite recently Reid, using a continuous injection technic, found the tolerance to dextrose of hypophysectomized-depancreatized cats to be even less than that of animals only depancreatized.

[6] The absence of morphologic abnormality of the islands of Langerhans in some cases of diabetes remains a mystery. Bensley has pointed out that the so-called beta cells of the pancreas normally contain granules, he has failed to find granules in a number of cases of diabetes, the space they should occupy being filled with fluid. According to Woodyatt, others find granules in the beta cells It is possible, he wrote, that the impairment of islet function represents a secondary change resulting from exhaustion rather than a primary lesion.

[7] Even Houssay admitted that "in all diabetes there is an insufficiency of insulin in relation to the needs of the organism" *He insisted, however, that "in all* [illegible]

of the thesis that the primary abnormality is that of insular mechanism [illegible] mechanism, when sound, is capable of meeting any demands that may be encountered from variations in blood sugar provoked by other factors

This article by Houssay is tremendously valuable as a review of the recent studies of the endocrine regulations of blood sugar It contains more than 100 references to experimental studies

PROVOCATIONS TO DIABETES

All those conditions, morbid or otherwise, which intensify a diabetes already in evidence likewise may precipitate diabetes in the predisposed. They are of two categories, including in the first place diseases which depress the insular reserve by grossly destroying the tissue of the pancreas, and in the second those dis- urbances of metabolism which, by creating a greater demand for nsulin, impose an added strain on the island cell.

In the first category are pancreatitis, acute and chronic (and rare cases in which pancreatitis is attributable to syphilis), pancreatic stone, pancreatic cyst, hyalinization and likewise fibrosis, secondary to chronic infection or to arteriosclerosis or simply to aging, and hemochromatosis. The lesion known as "hydropic degeneration" is a result of the uncontrolled disease and only secondarily is of etiologic significance.

In the second category the first place goes to obesity. Included also are all conditions of hyperactivity of those endocrine glands which function in normal opposition to the pancreas. They are hyperthyroidism, acromegaly, certain other types of hyperpituitarism, and the adrenal cortical syndrome. Here also should be placed those organic and functional disturbances of the central nd autonomic nervous system which, like the Claude Bernard puncture of the floor of the fourth ventricle, provoke glycosuria their significance in precipitating lasting diabetes, however, is disputed. Included also is climate, which Mills (1936) and Petersen point to convincingly as affecting both the incidence and severity of this and other diseases.

Lesions of the Pancreas.—Acute pancreatitis, destructive as it may be to pancreatic tissue, is not always followed by diabetes. Umber, according to Joslin (1937) in thirty-eight cases of infectious necrotic pancreatitis from which the patients recovered, found diabetes afterward in only seventeen.

Chronic pancreatitis frequently depends upon extension to the pancreatic ducts of infection of the biliary tracts. In fifty-ight necropsies on diabetic patients at The Mayo Clinic I found holecystitis in four cases and cholelithiasis in sixteen, or an incidence of 34.5 per cent with diseases of the gallbladder. In 245 cropsies on diabetic patients, Warren found cholelithiasis in ty-two and cholecystitis without stone in nineteen, or 33 per

cent with disease of the gallbladder. This incidence of cholecystic disease is at least three times that observed in necropsies on nondiabetic patients, and with other evidence, much of which is considered by Joslin (1937), it shows that diseases of the gallbladder not infrequently precipitate diabetes in the predisposed.

Allen has expressed the opinion that acute blood-borne infections are responsible for the fibrous changes that are seen in the islands and acinous tissue of the diabetic pancreas, and that diabetes may follow "from functional wear and tear," months or years after the original injury has been incurred.

Grauer found eight instances of an increased level of blood sugar in fourteen cases of carcinoma of the pancreas. No control could be established between altered levels of blood sugar and *liver weight, liver metastasis, common bile duct obstruction, or metastasis to other organs known to have a physiologic effect upon* the level of the blood sugar, but where the pancreas had been totally replaced by tumorous growths, or where excessive collapse of pancreatic tissue had occurred, or where diffuse fibrosis had led to extensive loss of parenchyma, a disturbance in the level of blood sugar was almost uniformly associated.

The frequent coexistence of diabetes and arteriosclerosis has led some writers to consider that the former is responsible for the latter, and others to take the opposite view. The relationship, however, remains undetermined. Occasionally the blood supply to the islands may be diminished sufficiently by arteriosclerosis to depress the insular reserve, but that this occurs frequently is made *unlikely by Warren's finding that only 5 per cent of 259 pancreases* of diabetic patients showed a marked degree of arteriosclerosis On the other hand, hyalinization of the islands of the pancreas occurred in 39 per cent of Warren's 220 necropsies on diabetic patients forty years of age, and in only 3.7 per cent of eighty necropsies in which the patients were less than forty years of age. It is not impossible that hyalinization depends upon disturbances of the blood supply in a manner analogous to the similar hyaline deposit in the glomerules of the kidney.

The other conditions falling in the category of lesions of the pancreas may be dismissed *without further comment.* Of principal significance in every instance is the fact that none of them, with the possible exception of hemochromatosis of the pancreas,

regularly causes diabetes. They destroy insular tissue, but in most cases the insular reserve is large enough so that the loss of insular substance is still compatible with adequate endocrine function.

Obesity and hyperthyroidism.—In cases of diabetes provoked by conditions in the second category the pancreatic islands may be normal in appearance. In them the insular reserve ultimately is exhausted by long-sustained demands for unusual amounts of insulin. The first place in this category goes, as I have said, to obesity. The incidence of diabetes among the obese is many times that found in persons who either are average or below average in weight.[8] The observation has been made the subject of many comments but has not been explained. The answer, I suggest, is this: When an adult man or woman adds to his body weight, his basal metabolic rate, as "B.M.R." commonly is expressed, remains within what are called normal limits; that is to say, the calories produced per square meter of surface are unaltered. Actually they may be moderately increased, but the important consideration is that the number of square meters to be reckoned with increases, and as the surface enlarges, the total basal heat production increases materially. At the same time the muscle mass and the size of the organs, with the possible exception of the heart, remain as they were before weight was gained. The increase in surface is attributable exclusively to adipose tissue, and since such tissue is very inert chemically and contributes only meagerly to the increased exchange of energy, the extra metabolism is nearly all thrown on the unchanged mass of muscle and organ. It formerly was supposed, incorrectly, that the metabolic rate was lower than normal in obesity. The contrary is the case; the metabolic rate of the chemically active tissues of the body, its muscle and organ mass, is increased to a degree which is quite as great as we

[8] The statistical investigations of the Metropolitan Life Insurance Company (May 1937) indicate that diabetes is eight times more common among persons who re 25 per cent or more overweight than among those of average weight, and thir-een times more common than among those who are underweight. "The most vorable build as regards mortality in general at the various adult ages in man is to age 30, slight overweight, ages 30 to 39, average weight ages 40 to 49, slight derweight; ages 50 and over, an appreciable degree of underweight." The report ely concludes with the admonition that, in working toward the goal of reducing incidence of obesity, care must be taken not to make the cure worse than the ase "It is noteworthy that the tuberculosis death rate has declined least among g women in the late teens and early 20's." There is reason to believe that the n for this is that resistance to disease has been lowered by foolish and unneces- dieting."

ever encounter in goiter. Incidentally, this is a very good reason for not using preparations of thyroid in the treatment of obesity.[9]

The incidence of diabetes among persons with hyperthyroidism is about 3 per cent. This figure, though not extreme, is at least three times that for the population as a whole and still higher than that for the nonobese population. Hyperthyroidism is a condition which, as is well known, seriously aggravates pre-existing diabetes. However, it usually is limited in duration, either spontaneously or by the intervention of a surgeon. The hypermetabolism of obesity is continued for a much longer period, and when strains and stresses are under consideration, the element of time is of great importance. It is little wonder that the obese die younger and are more susceptible than others to the degenerative diseases, including diabetes.[10]

[9] Duncan, Fetter and Durkin have clearly recognized the effects of changes in the rate of energy exchange on the insulin requirement in diabetes. Clinically, any factor, physical exercise excepted, which increases the rate of energy exchange *increases the need for insulin*. *The authors further maintain that these same factors* shorten the period of insulin effectiveness, so that doses of insulin must be spaced at shorter intervals. I am convinced, from clinical experience, that this generally is true, although satisfactory experiments to prove the point have not, to my knowledge, been performed.

Exceptions to the rule that factors increasing the rate of energy exchange increase the need for insulin are exercise and dinitrophenol. With exercise the explanation seems to be that the reaction glycogen⇄lactic acid and other reactions associated with the release of muscular energy take place without the intervention of insulin. With the stimulation of metabolism provoked by dinitrophenol insulin likewise may not be involved. Wishnofsky and his co-workers observed that the administration of dinitrophenol to diabetic patients did not increase their hyperglycemia, either in the fasting state or after the ingestion of dextrose, and Barker found that excretion of ketone bodies by completely diabetic dogs was not augmented by giving dinitrophenol. Bryan, Ricketts and Dine gave dinitrophenol to a depancreatized dog in doses sufficient to double the caloric production per hour without increasing the output of sugar. The animal received a constant diet in two feedings daily with 15 units of insulin at each feeding, and this regime remained unchanged throughout the observation. There also was no increased excretion of organic acids, nitrogen or creatinine. The absence of any change in the excretion of nitrogen in this experiment, as well as the constancy of the respiratory quotients, suggests that the metabolic stimulation of dinitrophenol is limited to stimulation of fat metabolism.

[10] An interesting parallel to these observations on obesity is the fact reported by the Metropolitan Life Insurance Company (July 1937) that tallness does not affect mortality. The study comprised 20 000 men who were 6 feet, 2 inches (188 cm) in height or more; the tallest was 7 feet, 1 inch (213 cm). Tallness, like obesity, involves increased surface area and, therefore, a high basal exchange of energy. The difference from obesity is that increased height is accompanied by an increased mass of muscle and organ tissue. Thus the basal metabolic rate, if calculated according to the mass of chemically active tissue, would not be different in tall persons from that of persons of average height and average surface area. In the group of tall men studied, the mortality from diabetes was normal both in the aggregate and in its distribution in weight and height groups.

The weather.—Dr. William F. Petersen, who has written extensively on the influence of the weather in disease, attempted to show that the meteorologic environment has much to do with the clinical course of diabetes—its onset, the character of its course and the precipitation of complications, as well as death. While I am quite unable to agree with some of his deductions, I will take this occasion to subscribe to his principal thesis. Diabetes, as Mills (1935) also has emphasized, is so much more prevalent in regions of the earth where climatic disturbances are severe that the correlation cannot be ignored.

Petersen said that: "given a suitable constitution and the hereditary background, the variable environment of the cyclonic tracks makes manifest metabolic deficiency, which under other conditions would remain adequate for normal needs." Diabetes rarely develops in the European in the tropics, whereas the person from the tropics, the Negro for instance, when he removes to the disturbed regions of the northern hemisphere is more susceptible than the European. Other factors, such as diet, economic pressure and inbreeding, undoubtedly are responsible in part for the high incidence of diabetes in Jews, but the climate may also be influential. The Jews normally were domiciled in the relatively stable Mediterranean littoral. They have pushed north into the storm tracks and, being ill-adapted, reveal unusual sensitivity to the more vigorous meteorologic environment of these regions.[11]

The following is a comment by Mills (1936): "Human capacity for response to climatic urging is now seen as a very definite factor in much of the physical side of life, but such capacity does not seem unlimited. Ominous and increasing signs of bodily and mental breakdown are apparent in the most stimulating regions of the earth. Certain of the metabolic diseases may well be taken as indications of overstimulation or exhaustion of one part or another of the body. Diabetes, for instance, represents an inadequacy of the islands of Langerhans to meet the level of activity

[11] Mills (1935) observed in Cincinnati that diabetes came on during the first or second winter in southern laborers (white as well as black) who were enticed northward by the higher wages paid in the decade following the close of the World War. They also suffered more than native Cincinnatians from other degenerative diseases, and exhaustion, nervous or physical, was particularly common. They appeared as though they were simply burned-out in the metabolic sense, they kept warm with difficulty in the more changeable weather and in many ways were unable to meet the exigencies of northern existence.

demanded by the high metabolic requirements of a vigorous life. Throughout most of the civilized countries that report deaths by cause, it has been shown that diabetes mortality is related to climatic stimulation, the disease becoming a major medical problem only in those regions having invigorating climates. Diabetic patients from the North almost invariably find their disease less troublesome and easier of control when they migrate to tropical or subtropical climates. Negroes show most strikingly this increasing severity of the disease toward the North, their death rate from it rising even more markedly than does that for the white population. In Europe, too, and in Australia, this relation of diabetes mortality to climatic drive is just as definite as in North America. Errors in diagnosis cannot be responsible for these observed differences, for highest rates are not always found where medical practice is supposed to be best.

"With diabetes it cannot be the level of sugar consumption that is responsible for the higher rates in stimulating areas. Rather would it seem to be the level of bodily activity demanded of the population in these areas, regardless of their level of sugar intake, that determines the frequency of pancreatic inadequacy Pancreatic load is related to total heat and energy needs of the individual, and therein lies its dependence on climatic drive."

The severe climatic disturbances in the northern states of the United States depend upon masses of cold air which periodically descend from the Arctic Circle through the valley of the MacKenzie River, to pass into the United States, just east of the Rockies, and proceed eastward in the zone roughly bounded on the south by the Mason and Dixon line and on the north by the Great Lakes. To my mind it is of very real significance that the Canadian provinces, Ontario and Quebec, which lie north of this zone, have a diabetic death rate which is only half that reported in the zone This seems to show that low temperature alone is not the weather factor of major importance. It more probably is the degree of variability of temperature, together with the degree of variability of other meteorologic factors, such as barometric pressure and relative humidity. Possibly, also, rapid changes in the ionization of the air are important. A very interesting graph in Petersen's book shows the index of barometric variability in juxtaposition to annual mortality for diabetes in Chicago and in

Illinois. With a single exception, following the year of the influenza epidemic of 1919, the years with low climatic variability from 1910 to 1935 correspond throughout with periods of decreased annual mortality from diabetes [12]

Much more knowledge must be obtained before the full significance of climate can be established, but enough information already is at hand to make it desirable to devote more attention to this subject than heretofore has been accorded This much at least can be said today, that the climate in the great storm track of the United States is relatively more stimulating than that south or north of it. The people who live in it live more actively, whether what they accomplish is more worth while, is beside the point. The effect may be like that of hyperthyroidism, in which characteristically, much of the hyperactivity of the patient is purposeless. The result I strongly suspect is comparable to what I have stated occurs in hyperthyroidism and obesity. The twenty-four-hour basal exchange of energy is increased, and this creates an increased demand for insulin, so that pancreatic decompensation ultimately follows in individuals possessed of less than normal insular reserve.[13]

Other precipitating causes.—In the category of agencies which place unusual demand on insular reserve, we also find such items as occupation, economic status, and an urban versus a rural domi-

[12] Mills (1934), emphasizing the regional differences in diabetes for the disease in the United States and the higher proportion of total deaths in the northern stormy area, pointed to the fact that in the region where the peak is reached, namely, Nebraska and Iowa, the population is younger than on the eastern seaboard. As the western population approaches the age level of the East, the crest of diabetes severity, he predicts, will advance further into the Northwest. Diabetes in the South and throughout the Tropics, is a mild, nontroublesome disease, rarely accompanied by acetone production, in sharp contrast to its characteristics in the region south of the Great Lakes and in New England In Quebec and Ontario, north of the storm track, the weather, although colder, is not so variable, and steady cold without warm interludes is not so stimulating The diabetes mortality rate is correspondingly lower.

[13] Mills (1934), commenting on the effects of fluctuations of temperature in the northern tier of states of the United States, pointed to Bismarck, North Dakota, which is "located in the heart of the world's most stimulating region, . . . where man m[illegible]
[illegible]
50–90° [illegible]
to avoi[illegible]
unable to bank his fires so quickly, man is driven to expend his excess heat as energy It is this constant battering of the weather changes which generates in man there the high level of bodily combustion which drives him into action What he does may not always be right, but do something he must"

cile. The usual explanation for all of these is that occupations which are better paid and circumstances which elevate the economic status of individuals, provoke a higher diabetes rate by increasing the chances for becoming overweight. However, not all urban and not all wealthy diabetics are overfed or physically indolent, and the possibility may also be considered that higher paid occupations and the mere possession of wealth, carry with them responsibilities of a type that lead to more or less continuous stimulation of the autonomic nervous system; that, thereby, the pancreas more frequently is called upon to place a break on the mobilization of glycogen and that this may constitute a strain, leading in the end, when the insular reserve is low, to a break in pancreatic compensation.[14, 15]

Sugar.—There is a great deal of difference of opinion as to whether a high consumption of sugar stimulates the development of diabetes in the predisposed. The evidence is equivocal. The level of the blood sugar is more rapidly raised by sugar than by any other food, and thus the pancreas intermittently is placed under a greater strain by sugar than by any other food. On the other hand, recent observations seem to indicate that sensitivity to insulin is increased by high carbohydrate meals, this perhaps being effected, as Marks has suggested, by inhibition of pituitary activity. Such a result might neutralize the injurious effect of the sugar. Himsworth expressed the belief that diabetes may be provoked by diets deficient in sugar. The per capita consumption of sugar is high in the United States, and a very high diabetic death rate accompanies it, but as Joslin (1937) has noted, our consumption of sugar has been stationary in recent years, and in Australia and Denmark, where the per capita consumption of

[14] Lombard and Miner, commenting on a group of diabetic histories studied in the Massachusetts Chronic Disease Survey, found the association of a nervous temperament to be next in importance to obesity. The significance, measured by the table of "t" of R. A Fisher, was 6.9 for overweight of 20 per cent or more, and 6.00 for a nervous temperament For little exercise it was only 2.65. *For heredity it* was 4.61

[15] Woodyatt lays more emphasis than do others on nervous and emotional factors in the etiology of diabetes He wrote "Severe nervous shocks, such as may result from injuries, exposures, etc., precede the onset of diabetes in a not inconsiderable fraction of cases The same is true of physical shocks and severe emotional disturbances Depressive emotions, anxieties, fears, unhappiness arising from various causes—such as domestic infelicities, financial losses, etc., are notoriously capable of provoking the onset"

sugar is greater than here, the incidence of diabetes is relatively low.[16]

Other endocrine glands.—The category of factors creating more work for the pancreas includes those conditions in which we have to deal with an oversupply of any of the group of hormones normally antagonistic to the action of insulin. Hyperthyroidism already has been considered, and I have referred to tumors of the pituitary, and to adenoma and carcinoma of the adrenals. We also may have to deal at times with cases of diabetes in which hyperfunction of those glands, not accompanied by conspicuous anatomic abnormality, is responsible for aggravation of intensity I have been on the lookout for clinical examples of such conditions but have encountered very few of them. One of my assistants, Dr Rushton, observed that the blood plasma of certain diabetic patients will antagonize the hypoglycemic action of insulin if injected with insulin into normal rabbits The procedure is one which has been described by de Wesselow and Griffiths. In a case of diabetes in which a very significant resistance to insulin developed concurrently with symptoms of the menopause, an assay of urine revealed an excess of prolan and no estrin. Administering large doses of estrin in this case reduced the requirement for insulin from 90 to 50 units a day. Blood plasma originally obtained from this patient and injected with insulin into rabbits inhibited the action of the insulin Later, when the patient had been treated with estrin, her plasma was no longer inhibiting The observation supports the suggestion that, in this case, pituitary hyperactivity, provoked by the menopause, was responsible for resistance to insulin The procedure of de Wesselow and Griffiths unfortunately seems not sensitive enough to reveal many examples of diabetes exaggerated by menopausal hyperpituitarism That hyperpituitarism occurs in the menopause more frequently than Dr Rushton was able to demonstrate is strongly suggested by the general beneficial action of estrin in the treatment of other symptoms of the menopause, as well as by the

[16] [illegible]

undoubtedly will receive more attention in the near future as appreciation of the importance of a more liberal supply of these catalytic agents becomes established

rapid increase of the incidence of diabetes in women after the change of life.[17]

HEREDITY IN DIABETES

Authorities have been commenting for years on the relatively high incidence of diabetes in the families of diabetic patients, but we owe to Pincus and White the first satisfactory study of the significance of this. They found that both twins contracted diabetes in 70 per cent of sixteen pairs of similar twins, as compared with only 10 per cent of diabetes in both twins of a series of dissimilar twins. They found also that diabetes occurred nearly seven times more often among the parents and siblings of diabetic patients than in the relatives of a large group of nondiabetic patients. They searched for latent cases by sugar tolerance tests and random determinations of blood sugar and obtained "statistically supernormal" blood sugars in 25 per cent of the relatives of 169 diabetics, and in only 2 per cent of 125 control individuals. They then investigated the mendelian recessive ratio in a series of consecutive cases of diabetes, and found, when allowances were made for certain factors which were known to alter expectations based on this ratio, that the identified ratio closely approximated the expected one. According to the mendelian pattern for a recessive character, a cross between two diabetics should give diabetes in 100 per cent of the offspring; a cross between a diabetic and an hereditary carrier should give diabetes in 50 per cent, and a cross between two hereditary characters should give diabetes in 25 per cent. The incidence of diabetes observed, in the three types of crosses, instead of being 100, 50 and 25, respectively or even 100, 40 and 16, after correction was made for selection of cases, was 24, 10 and 4. However, the authors explain that deaths of individuals before they reach the age of the peak of diabetic incidence account for the smaller numbers, and that the similarity between

[17] Gessler, Halsted and Stetson, of the Thorndike Memorial and Harvard University, reviewed the literature bearing on the effect of administration of estrin on experimental and clinical diabetes, and reported observations on five diabetic women, past the menopause, to whom they had given daily intramuscular injections of 50 000 international units of estradiol benzoate A significant lowering of the fasting blood sugar resulted in two of the cases in which the onset of the [illegible]

years, in the other the diabetes had preceded the menopause

the ratios expected and those found is the significant feature of the observation The figures 4, 10 and 24 are in the ratio 1:2.5:6, and the expected ratio, corrected for the mode of selection, namely, 16:40:100, is the same, namely, 1:2.5:6.

I am not sufficiently trained, either in statistics or eugenics, to be able to pass final judgment on this evidence, but it impresses me as being of more importance than anything else that we know about diabetes If it is not adequate, the subject cries aloud for further study, because if the conclusions of Pincus and White are correct, it means that the biologic inferiority upon which diabetes depends is transmissible, not only by diabetics, but also by the siblings of diabetics.

Joslin (1938) apparently accepted the conclusions of Pincus and White, but has been unwilling to draw from them the obvious inference.[18] The prevention of diabetes, he said "depends upon controlling one's heredity. Obviously that cannot be done." We should think twice, he added, before recommending the "mass sterilization" that would be required to eliminate diabetes However, although heredity cannot be controlled, posterity certainly can be, and mass sterilization is not called for to do it. Probably all that would be necessary to prevent the spread of diabetes, in this day of enlightenment on the subject of birth control, could be accomplished by an extensive program of education.

PREVENTION

Until we have sufficiently reliable information to justify a campaign to limit the families not only of diabetics, but also of the children and siblings of diabetics, we must do what is possible to protect those individuals whom we assume to be predisposed

[18] In summarizing the findings after extensive studies of the histories in many thousand cases of diabetes, Joslin and his associates reported that 24.5 per cent of the patients gave a positive family history Higher percentages were found in special groups, for example, in women as compared to men (women take more interest in details of family history), in recent cases as against earlier cases (advance in incidence of the disease?), in physicians as compared with laymen, in Jews as compared with Gentiles (29.6 per cent) The percentages of diabetic patients with a positive family history of diabetes are far higher than controls Thus, taking parents between the ages of thirty and fifty-nine, 8.6 per cent of the parents of diabetics were also diabetics, compared to 0.5 per cent of parents of nondiabetics Referring then to the work of Pincus and White, the authors concluded that the theory of recessiveness accords best with the available facts Joslin's objections to restriction of childbearing by diabetics are elaborated in a paper published in 1938

because of consanguinity with diabetics. For them we can advise correction of abnormalities now recognized as precipitating factors in the disease; medical and surgical attention to chronic infections of all kinds, early thyroidectomy for hyperthyroidism and for adenoma of the thyroid, which so frequently leads to hyperthyroidism, and avoidance of obesity, or if the individual already is overweight, correction of this by a safe, effective course of *reduction.*

Something even can be done about the climate. Mills (1936) suggested vacationing in the South for inhabitants of northern regions with a vigorous climate. Unfortunately, few people will be able to follow such advice and the time of vacations probably is too limited to accomplish anything substantial thereby. More to the point would be change of residence to the south, preferably *to the tropics. A nationally organized and strongly financed* Public Health Association might undertake to assist diabetics and their siblings by finding employment for them in the South, thus perhaps preventing their children from developing the disease.

These means for combating the increasing incidence of diabetes should not be neglected, but to my mind real progress will not be made merely by protecting the predisposed. What we *must aim at primarily is the prevention of the predisposition.* An organ inferiority is at fault, involving deficient insular reserve, and if this constitutes a characteristic transmissible by inheritance, as there is every reason to believe and as the evidence of Pincus and White may have proved, the size of diabetic families must be *limited. It is not necessary to demand "mass sterilization"* or even to ask that members of diabetic families voluntarily remain childless. If such persons would limit their families to one child or even two the same result would be accomplished, since for a family to survive, the number of children in each generation must exceed three.

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CHAPTER IV

PROGNOSIS AND COURSE OF DIABETES

The prognosis in diabetes, the course of the disease and the essentials of effective treatment are topics which properly may be considered together in this and the following chapter. The first two, in all but very mild cases, largely depend on the third.

FACTORS GOVERNING PROGNOSIS

Factors affecting prognosis may be classified as follows. Several of them, as readily will be seen, are interdependent:

1. Early diagnosis in acute cases.
2. The severity of the diabetes.
3. The age of the patient.
4. The availability and effectiveness of insulin when required.
5. The adequacy of the diet.
6. Intercurrence of complications.

1. *Early diagnosis.*—Among the most tragic experiences in the practice of medicine is the rapidly fatal, stormy course of untreated diabetes with acute onset. Such cases, for the most part, are those of children or young adults, and in them, through ignorance or because of the remoteness of physicians, experienced medical help all too frequently is not obtained in time to prevent the development of coma. An instance of this kind was the following:

A woman, twenty-two years of age, had returned from a holiday excursion five days before, apparently in perfect health. That evening she fell ill, and although symptoms of diabetes developed, they were not recognized and the summoning of a physician was delayed for four days. Even then valuable time was lost through the physician's not finding sugar in the urine until the morning of the fifth day. When we were notified the patient had been almost unconscious for more than eighteen hours and, as frequently happens when treatment is delayed in diabetic acidosis, the patient died. The therapy instituted was enough to bring the glycemic level to normal and to restore to normal values both the electrolytes and the carbon dioxide com-nning power of the plasma. Another case that remains vividly in my emory is that of a child two years of age, brought in from the country after

an illness lasting only two days This was before we had insulin and death followed in six hours, in spite of administration of sodium chloride and sodium bicarbonate.

As evidence that early treatment can prevent fatalities, even in fulminating instances of diabetes of acute onset, I may cite a case in the family of a girl twelve years of age who lived on an isolated ranch in the Northwest and died before the physician could help her. *The illness had lasted only three days.* The physician arrived when the child was moribund, and the family first learned what was wrong from him. The memory of this girl's early symptoms was still fresh in the minds of the parents when three months later the twin sister of the child—an identical twin—fell ill with the same disease. She was brought at once to Rochester and, within forty-eight hours of the onset, although by then severe acidosis had developed, treatment was started This twin was known to be living many years later and her diabetes, although severe, was not extremely severe. Identical twins, as is well known, normally develop the same diseases, and when they do, the severity and course of the affection usually is the same. Thus it may be presumed that the first child might be alive today if treatment had been instituted early enough.[1]

2. *The severity of the diabetes.*—It has been our practice for many years to classify patients with respect to the severity of what may be called the "underlying metabolic abnormality." This classification is as follows:

Grade 1 includes those mild cases in which the condition is readily controlled by omitting sweets from the diet. The incidence of this mild grade of diabetes among new patients whose

[1]"Diabetes is an out-and-out chronic disease, but it must not be forgotten that the first years of diabetes following the discovery of the disease truly are the diabetic's danger zone It is a triumph of modern medicine that the greatest mortality from diabetes is being transferred from the first years following its onset to later years The first years of a diabetic's life should be his safest and not the most dangerous, as was true a few years ago, and deaths in the early years should be regarded as preventable accidents." (Joslin).

Naunyn, after citing a number of cases of acute, fatally progressing diabetes, *commented, in 1906, that such cases did not necessarily represent severest diabetes,* and cited others of equally acute onset in which early treatment was secured and the later course proved relatively mild Examples of this now occur over and over again The important thing is early recognition and prompt attention Delay is fatal Fortunately, even in children the course of untreated diabetes frequently is chronic—in adults usually it is very chronic—so that ample time is allowed for its recognition and treatment.

disease is diagnosed as diabetes at The Mayo Clinic has been about 32 per cent.[2]

Grade 2 includes cases of such mildness that control can be maintained without insulin, provided the dietary restriction applies not only to sweets but also to starches, and that the daily intake of carbohydrate is held somewhat below 150 gm. The incidence of cases in this group has been about 19 per cent.

Grade 3 includes those cases in which the patients cannot be maintained in satisfactory equilibrium with diet alone, but require not more than 30 units of insulin daily. The incidence of cases in this group has been about 30 per cent.

Grade 4 applies to cases in which more than 30 units of insulin are required daily. The incidence is about 14 per cent.[3]

Recently we have added a grade 4+ for cases in group 4 which are difficult to maintain because of unusual instability. The number of these cases has been increasing in recent years. For the most part the patients are children, but some are adults, and among the latter are a few women of the menopause age, also a few men in the same period of life.

Much overlapping occurs between these groups, and any one patient may be found in one group at one time and later in the group above or below. The classification, nevertheless, is helpful, and in general provides some guidance in the matter of prognosis, providing the decision about the grading of the case is postponed until the patient has been under observation during a period when his disease is not aggravated by intercurrent infections or other remediable complications. It at least is a safer guide than the quantity of sugar in the urine or the percentage of sugar, fat or acetone (diacetic acid) in the blood, since these signs are transient and depend altogether on what treatment has preceded.

What we attempt to classify is the character of the diabetes which, as Umber has noted, tends to remain more or less the same

[2] This group corresponds to that Naunyn called "alimentary glycosuria e saccharo." Differentiation from nondiabetic glycosuria now depends on the finding of an accompanying hyperglycemia, and from toxic glycosuria, such as is provoked by infections and various narcotics, on a longer duration (permanency). Cases in our grade 2 Naunyn would have classified as "glycosuria ex amylo."

[3] Naunyn's differentiations of types of glycosuria might well be extended to a third type applicable to many cases of our grade 3 and all of those in grade 4 which could be called *glycosuria ex proteine* to indicate that limitation of sugar and starches does not suffice to prevent the excretion of dextrose since the tolerance is so low that sugar derived from the metabolism of protein is incompletely utilized

whether mild or severe. "Neglect of diet or insulin," he wrote, "as well as infections, may aggravate the severity of mild cases to such a degree that coma, even death in coma, may result. Formerly we thought that the severity of the constitutional disease was recognizable by the degree of intensity encountered. That, however, is wrong. Today we have learned that even the severest and formerly fatal variations of intensity can be corrected, even many times, so that after a shorter or longer time the disease assumes again an originally milder character and the patient becomes as well and effective as he was before the period of exacerbation."

The severity of the diabetes, as indicated by the foregoing classification, is of prognostic significance, to the extent at least that the danger of acidosis is greater in the higher grades. Treatment, therefore, in cases in the higher grades must be conducted with correspondingly greater precision, and the penalty for carelessness in these cases is correspondingly more severe.[4]

3. The age of the patient and prognosis—Formerly it frequently was stated that diabetes acquired before the age of forty years was severe, while that acquired later in life was mild, but such a rule is unreliable. Before insulin became available, the diabetes of children almost always was fatal. This probably is attributable to the relatively greater ease with which ketosis develops among children than to the actual severity of the underlying metabolic disturbance, for, since insulin has been at hand, the diabetes of many children falls into group 3 (requiring 30 units of insulin or less) and some even into group 2, and remains in these groups indefinitely. However, the diabetes of a disproportionate number of children is of group 4 and a poorer prognosis for them is still in evidence. This is apparent from Joslin's table (Table 1), which reveals that after the onset of diabetes the

[4] Naunyn commented that there is no reason to believe that the milder forms of diabetes differ in any fundamental way from those more severe On the contrary, any such difference is denied by the fact that mild diabetes may become more severe

The patients with diabetes grade 3 and especially those with diabetes grade 4, are most endangered by the lure of advertising promoters of "cures" without dieting, or oral remedies to replace hypodermic injection of insulin Milder diabetes frequently responds favorably to the dietary advice that invariably accompanies whatever hocus-pocus is being advertised Patients with more severe diabetes, hearing of these benefits, are led thereby to place their trust in what proves for them to be a chimera.

TABLE 1

AVERAGE DURATION OF LIFE SUBSEQUENT TO ONSET OF DIABETES AMONG DECEASED EX-PATIENTS IN EACH OF THE IMPORTANT ERAS OF TREATMENT BY AGE GROUPS AT ONSET (EXPERIENCE OF ELLIOTT P JOSLIN, M D, 1898–1935)*

Age periods of onset.	Naunyn period, before June, 1914		Allen period, June, 1914 to Mar 16, 1922.		Early Banting period, Aug 7, 1922 to Dec. 31 1925		Middle Banting period Jan 1, 1926 to Dec 31, 1929		Later Banting period, Jan. 1, 1930 †	
	No of cases	Duration, yrs	No of cases	Duration, yrs	No of cases	Duration, yrs.	No of cases	Duration, yrs	No of cases	Duration, yrs
All ages	331	4.8	597	6.0	514	7.6	897	8.4	931	11.0
0–9	25	1.2	47	2.7	14	2.6	9	3.1	13	7.4
10–19	39	2.9	69	3.3	30	3.6	22	4.0	29	6.5
20–39	80	3.9	162	5.5	92	7.3	101	10.5	117	16.7
40–59	137	6.9	216	6.1	202	9.4	515	9.6	516	12.3
60–89	50	4.5	103	6.1	116	5.2	250	5.7	304	7.1

* Prepared by the Statistical Bureau of the Metropolitan Life Insurance Company
† Deaths recorded up to March 13, 1935

duration of life among children who died continued to be less than half as many years as that among adults between the ages of twenty and fifty-nine years.[5]

4. Availability and effectiveness of insulin (insulin resistance). —Before the insulin era prognosis in diabetes depended primarily on the fundamental severity of the disease. Therefore, the lives of affected children were tragically short, as is evidenced in Table 2. This was true even when the best possible dietetic treatment

TABLE 2

FATALITIES IN CASES OF DIABETES OF CHILDREN ENCOUNTERED IN THE MAYO CLINIC IN THE PRE-INSULIN ERA

Dates of registration, inclusive	Cases.	Deaths.	Mortality per cent.	Duration in months of diabetes in fatal cases.		
				Minimum	Maximum.	Average.
October 1, 1919–Sept. 30, 1920	11	9	82	4	36	17
October 1, 1920–Sept 30 1921	11	9	82	2	47	17
October 1, 1921–Sept. 30, 1922	10	4	40	10	23	18

[5] On the other hand, in another table Joslin reveals that the approach to normal life expectancy has been practically the same from childhood to old age At ten years of age the normal child has an expectancy of fifty seven years, but the diabetic child one of thirty-two years This is 56 per cent of the normal expectancy At sixty years of age the normal man has an expectancy of fifteen years, while for the diabetic patient the expectancy is nine years, representing 60 per cent of the normal expectancy

was given. On the other hand, even before the insulin era, patients now classified by us as in group 1 might live for decades and often did so with little or no dietetic supervision. Patients with these milder forms of diabetes frequently are little disturbed by their infirmity, except when the intensity of the process is aggravated by an *intercurrent complication of one kind or another*. Patients with mild diabetes in the later decades are subjected, however, to additional risks ushered in by arteriosclerosis, indeed, their susceptibility to arteriosclerosis seems to be quite as great as that of patients with fundamentally more severe diabetes.

Insulin, as is well known, has reversed this prognostic picture; its use almost eliminates the necessity for diabetic deaths of children and other patients, and usually prevents acidosis secondary to infections and other complications. Unfortunately accomplishment still falls short of what today is possible. Many patients requiring insulin fail to receive it for one reason or another, and hence deaths from diabetic coma—preventable, inexcusable deaths—continue. The physician in general is still insufficiently informed about how to prescribe insulin, and in occasional tragic instances even advises against its use. This was pointed out in Minnesota by my former assistant, Dr. Stafne. On the other hand, physicians who themselves are diabetic have had an enviable health record, as is evident from the experience of Joslin, who made the comment that death from coma, of a physician, is now almost unknown [*]

Prognosis affected by sensitivity to insulin; insulin resistance.—Sensitivity to insulin varies greatly even in persons who have no diabetes, as has been shown by the wide variation in the doses of insulin necessary to provoke hypoglycemia in patients under treatment for schizophrenia (Rosenberg and associates). Similarly, some diabetic individuals are more sensitive than others, as has

* "In private practice the physician should know how to maintain the severest case of diabetes year in and year out completely able to work and free from sugar In spite of all this, large statistics reveal that the total mortality of diabetes has not diminished since insulin came The paradox is a challenge for better organization What good organization can accomplish is taught by examples such as Stettin's [the city of Stettin, Germany], where thanks to effective care of diabetes the number of cases of diabetic coma for many years has been brought almost to nothing The experience in the diabetic home at Rügen may also be recalled, and the results of Buttner-Giessen. It is apparent that the health service must attack this problem in co-operation with clinicians" (Nonnenbruch)

been shown especially well by MacBryde and Himsworth. In general, sensitivity to insulin is found in the younger patients and those who are thin, whereas insensitivity occurs in those who tend to be obese or who have hypertension. This relatively moderate variability of response to insulin probably can be explained by differences in the intensity of action of the normal antagonists to the action of insulin—pituitary, adrenal, thyroid—acting directly on the liver or other tissues, or indirectly on the liver through the nervous system.[7] Greater insensitivity is observed as a result of many infections.[8] Also markedly affecting sensitivity is diabetic acidosis, the result of which may be an insulin resistance that persists for many days after the acidosis has been completely checked. It is not improbable that the liver is principally at fault in many of these cases of more marked insensitivity to insulin, because, as is well-known, degenerative parenchymatitis results from draining the liver of glycogen and filling it with fat, and in diseases affecting the liver marked resistance to insulin occasionally is encountered. A patient with mild diabetes on my service at the Billings Hospital, Chicago, developed thrombosis of the hepatic artery. This was accompanied by a sudden enormously increased requirement of insulin. The case was described by Pollack and Long.

Mild degrees of insensitivity to insulin are not disturbing from the standpoint of management or prognosis, but when true resistance to insulin develops, enormous doses of insulin may be required to prevent acidosis. Fortunately the complication is unusual. In a case reported from The Mayo Clinic by Allan and Constam, the patient suffered from hemochromatosis with marked cirrhosis of the liver and ascites. A similar case was described by Root. On the other hand, neither hemochromatosis nor hepatic cirrhosis consistently leads to this abnormality. Cases have been

[7] Thus, de Takats, Fenn and Trump showed that the sensitiveness to insulin was increased by celiac ganglionectomy in cases in which relative insensitivity preexisted. Illustrative of the possible influence of the anterior lobe of the pituitary is the previously cited case of insensitivity developing during the menopause and controlled by administering estrin (see p. 51).

[8] The observation of Bürger and Kohl, that the neutralizing effect of blood serum on insulin was attributable to an enzyme-like factor neutralizable by heat, and that blood containing many leukocytes possesses greater neutralizing power, may have bearing here, although more probably the effect of infection on the liver and tissues is the principal factor.

seen in which insulin resistance accompanied destructive pan atic disease, but pancreatectomy in animals usually increases se tivity to insulin and extensive pancreatic disease can exist v relatively benign diabetes. Insulin resistant diabetes has b described in cases of hyperthyroidism. In this situation an planation is available. In the so-called thyroid crisis the b metabolic rate probably is enormously elevated and the rate destruction of insulin very probably is accelerated. Discovera explanations for insulin resistance may be entirely absent. A f of importance is that occasionally at a certain stage in the progr of the condition, sensitivity to insulin may return, and for t reason as much insulin as may be required to control acidc must be used, no matter how high the doses must be pushed. T number of units given in some cases is almost incredible. Rathe and Froment in such a situation used 2,170 units in twenty-fo hours.[9] To be considered, also, in the treatment of insulin sistance, particularly if hepatic disease is suspected, is the admi istration of large doses of dextrose, as advocated by Ellis.

A high degree of insulin insensitivity was found by Martin three experiments in which depancreatized dogs were deprived vitamin B complex. After five to seven weeks, despite the co tinued administration of previously adequate doses of insulin, tl blood sugar was elevated and intense glycosuria developed. A first this could be corrected by increasing the doses of insulin, bu later even very large doses (eight times those originally effective proved insufficient to suppress the glycosuria In two of the ex periments the disturbance was corrected by administration c vitamins, in one by the intramuscular injection of vitamin B and B_2 in the form of betaxin and lactoflavin. Betaxin alone wa

[9] In Root's case of insulin resistance 1,680 units were given daily. In a cas reported by Wiener the daily dose of insulin exceeded 3000 units Rathery an Froment apparently obtained some benefit in one case of insulin resistance b roentgen irradiation of the pituitary Prior to treatment the patient was receivin 300 units of insulin a day, in spite of which he was excreting daily 98 to 175 gm of dextrose and 11 to 31 gm of beta-oxybutyric acid After treatment 145 units o insulin a day was sufficient to maintain control (9 5 gm of sugar in the twenty fou hour urine and no acetone). The patient showed bronzing of the skin and th liver extended three or four fingerbreadths below the costal margin Another un usual case of insulin resistance has been described by Marble The only pathologi abnormality that could be verified was a chronic rheumatoid arthritis In this cas at a later time six roentgen treatments to the hypophyseal region—one treatment each day for six consecutive days (total of 1200 roentgen units to a field 6 by 6 cm in each temporal region, 400 K.V.)—were without effect.

ineffective. Lactoflavin alone was not tried. The author concluded that the action of insulin appears to depend on the presence of the vitamins of the B complex.[10]

5. *Adequacy of the diet and prognosis.*—Diet is to be the subject of a later chapter, but a word about its bearing on prognosis is indicated. Statistical evidence of the advantage, or otherwise, of the various types of diet prescribed by different authorities has not been assembled, but there is good reason to believe that in the effort to obtain control of glycosuria unnecessary restrictions frequently are enforced, with consequent impairment of the nutrition of patients and their subjection to disorders of nutritional deficiency, including increased susceptibility to tuberculosis and other infectious diseases The availability of commercial insulin permits a shift in emphasis in the matter of the diabetic diet from what is best for the control of the disease to what is optimal from the standpoint of the nutrition of the patient. There is no good reason for supposing that the nutritional requirements of diabetic patients are any less than those established for persons who are well.[11]

By the same token it is perfectly obvious that if the patient is neglectful of the ordinary care which he must exercise in the selection of his foods—since the amount of food must be balanced satisfactorily against the amount of insulin administered—or if he

[10] Reference is made in this article by Martin to the observation of Schroder that in general the vitamin requirement in human diabetes is greater than normal Also referred to are observations reviewed by Collazo and Pi Suñer Bayo indicating that in otherwise normal animals B-avitaminosis leads to disturbances of carbohydrate metabolism—depressed tolerance for carbohydrate, increased blood sugar, impoverished stores of glycogen in liver, muscle and heart and diminished sensitivity to insulin.

[11] Sindoni analyzed the dietetic habits of eighty-five diabetic patients who had been under treatment for from three weeks to twenty-seven years before coming to his metabolic department in the St Agnes Hospital, Philadelphia, and obtained evidence of hypovitaminosis in the dietary history, the symptoms and physical disturbances of every one of them Wiegierko properly emphasized that physicians frequently neglect other serious affections in cases of diabetes "Efforts directed against the diabetes have as an object the complete disappearance of glycosuria and depression of the level of the blood sugar To obtain this the physician often prescribes a regimen poor in calories and poor in carbohydrate Such a procedure is injurious for patients affected with other disease There are cases in which the [illegible]

the patient and not to cause disappearance of glycosuria and hyperglycemia"

is too ignorant to be properly educated in these matters, the difficulties of successful treatment are aggravated and the prognosis accordingly is affected unfavorably. Joslin repeatedly has emphasized that diabetic patients must have brains and must use them, and Nonnenbruch has stated: "It is necessary for effective treatment of a case of diabetes to have an intelligent patient, a wise physician and a clever cook. The imprudent or stupid patient *cannot be helped.*"

On the other hand, I wish to urge physicians, and others who are undertaking the instruction of patients, not to be discouraged too easily by apparent stupidity It happens time and again that individuals with no more education than permits them to read and write with difficulty and who at first seem hopelessly incapable, later respond satisfactorily and learn how to take excellent care of themselves, or of their diabetic children. This especially is true of underprivileged persons whose intelligence is obscured by their shyness and consequent embarrassment. The results obtainable with natively intelligent poor people usually are superior to those obtainable with educated and privileged, but undisciplined, individuals. In the case of patients who must be communicated with in a foreign language that is unknown to the instructor, the difficulties multiply, but even then excellent results can be had with the help of interpreters. More than one of our successfully instructed patients has been deaf and dumb.

6. Intercurrence of complications.—When their metabolic abnormality is under control and their diet is adequate nutritionally, diabetic patients seem to be no more susceptible to infections than others. Their surgical wounds heal normally if the local circulation is not impaired by arteriosclerosis Their colds are not unusually frequent, and the incidence of tuberculosis is low. On the other hand, infections cannot always be avoided and the danger that accompanies them is aggravated by the fact that *usually the severity of the metabolic abnormality is* intensified by them. If the life expectancy in our treated cases of diabetes must perforce remain lower than normal, this will be due principally to the greater danger accompanying infections, pregnancy, hyperthyroidism and surgical operations, also to the relatively higher incidence of occlusive sclerosis of the arteries of the heart and feet

The undernourished are predisposed to tuberculosis, and di-

abetics of the era before insulin, ill-fed by necessity, frequently contracted tuberculosis. This disease is much less common today, and yet the incidence of it among diabetics remains too high Either carelessness on the part of the patients in controlling their disease or the type of diet they have been told to take, must be responsible. The widespread teaching that diabetic diets ought to be low in fat and restricted in calories is open to criticism on this score. The incidence of tuberculosis among patients whose diets have been prescribed by us has been only 1 per cent, which compares favorably with that of the population at large in Minnesota Baker, studying diabetic coma among our patients, traced the subsequent course of eighty nine of them. One was reported to have died from spinal meningitis but, in view of the fact that he was suffering from active pulmonary tuberculosis when under our observation, death more probably can be ascribed to tuberculous meningitis This patient apparently was the only patient in the entire series who had tuberculosis, either before or after one or more attacks of coma

DIABETIC CURES

From the preceding discussion of the prognosis and course of diabetes it is apparent that the outlook in any but the milder cases depends primarily on the effectiveness of treatment If treatment is adequate, barring, in older groups of patients, accidents related to associated arteriosclerosis, life expectancy ought to be as long as that for the population as a whole. Also, the general healthiness of the individual ought to be normal. In the large majority of cases vigorous minds and sturdy bodies are obtainable; the adults can pursue their usual occupations with customary energy and the children develop normally, attend their schools and enjoy their play.[12] On the other hand, to encourage the hope of com-

[12] Only those of us whose experience extends back to the tragic era that preceded the discovery of insulin can fully realize how much has been accomplished by that discovery As an illustration of the far-reaching effect of saving lives otherwise doomed, I have abstracted the following from a contribution by Rosenfeld, a well-known critic of modern painting "Thanks are due to the discoverers of the efficacy of insulin at the very least for one American force This is the painter, whose representations of the inner life of American things now adorn the walls of the Whitney Museum in New York It is Charles Demuth As an artist Demuth came into being but a few years before he sickened dangerously with diabetes . . When the war drove him home [from his studies in France] Demuth returned with a few sensitive water colors They were the first original work of a man destined

plete recovery from diabetes is unjustified at the present time. Undoubtedly recovery may occur, more particularly in cases of acute onset in children and young adults, but the incidence of these occurrences is so minute as to be insignificant. By this I *do not mean that marked improvement of tolerance for carbohydrate* is not observed. The contrary is true in a very large number of cases of all degrees of severity.

It should be emphasized that transient remission of intensity is characteristic of the early diabetes of children and young adults provided some treatment is given At this time the treatment may be far from perfect—indeed, in some cases all that is required to control the glycosuria may be some simple dietary. The patient or parents are overjoyed, the physician is pleased, but the hope aroused is false In the course of a few months or in a year or two the intensity of the disease again increases and then to omit adequate treatment is to invite a tragedy. It is important to warn patients, and if they are children, the parents, to avoid being lured into a false feeling of security by the early benign *course of diabetes. Even with the exercise of the greatest* possible efforts to maintain a normal blood sugar level, later exacerbation, necessitating the use of insulin, is to be expected in almost all cases of diabetes in the young.

Joslin arbitrarily has proposed the following standards to which reputed cures for diabetes should conform. Very few cases

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to become an important agent of American self-consciousness And during the next few years he commenced developing his very personal art . . A deal of the scope of Demuth's feeling was already intelligible from this work of the years anterior to his crisis. Had he died [in 1919] . . . as in the Armistice year it appeared that he must do, we should be the poorer for an important force . . . Only a few of the strong, high-pitched Bermudan landscapes denote the dawning mastery. But Demuth lived on upward of fifteen years During [shortly after] the war the value of insulin had come to light Reprieved, almost as much a well man as he had ever been, . . . Demuth once again hobbled socially through the world . . . Thus, Demuth stands among the giant clan. Other artists possibly have given America a [illegible] of his own church or factory turrets in blue and in gray weather, shapely, [illegible] serene among the high agents of communal life"

Another dramatic illustration of the far-reaching influence of the discovery of insulin is provided by the rescuing from premature certain diabetic death of the Nobel Prize Winner, Dr George Minot Dr Minot later was able to contribute importantly to the discovery of the effective treatment of pernicious anemia, and thereby prolonged other valuable lives to add to the sum of values of communal life.

will be found that will conform. One in my experience deserves notation because for some years we thought a cure had been obtained. The patient, a young physician, had been very well until one day he noted unusual thirstiness and the same evening stickiness of his dried urine. This prompted him to test his urine for sugar and led to finding intense glycosuria. The following morning the fasting blood sugar was more than 0.300 gm per 100 c.c Treatment was instituted at once, and very rigid control of the glycemia was maintained for the next several years by means of diet and insulin. After five years the use of insulin was discontinued entirely, and after seven years the diet was augmented in its content of food so as to be almost a general diet. The fasting blood sugar and the determinations of blood sugar made before and after meals for some time remained perfectly normal, but still later hyperglycemia returned and insulin again was necessary.

The Joslin standards of diabetic cures—These are as follows:

1. Diagnosis.—The diagnosis of diabetes shall be based on a glycosuria of 0 5 per cent or more, accompanied by a fasting blood sugar of at least 0.14 per cent or a venous blood sugar after a meal of at least 0 17 per cent.

2. Duration of proved diabetes—The duration of proved diabetes, by repetition of the tests described under diagnosis, shall be recorded in months By this plan the individual can be classified as a proved diabetic of one or more months' duration. The longer the duration of the proved diabetes, the greater the respect which will be attached to its cure. Chance glycosurias and hyperglycemias resulting from errors in the laboratory, from operative procedures and from temporary infections, thus would be ruled out. Hyperthyroidism and hyperpituitarism would not be excluded and, therefore, a statement on these conditions should be included in the report of the case.

3. Test for recovery.—Glycosuria and hyperglycemia shall be absent, while the patient is without diabetic medication, both before and an hour after a meal. This meal must contain at least two fifths of the carbohydrate for the day. The carbohydrate for the twenty-four hours shall comprise at least two-thirds of the calories necessary to provide 30 calories per kilogram of body weight. Better still, the carbohydrate tolerance shall be unimpaired as judged by a normal glycemic curve following the oral

administration of 60 to 100 gm. of glucose to the patient in the postabsorptive stage.

4. Establishment of recovery.—A proved case of one or more months' duration, in which tests for recovery at the beginning and end of an interval of five or more years indicate recovery, shall be considered cured.

Physicians with experience in diabetes have felt that well-trained diabetic patients ought to be able to live normal lives, and that most of their patients did. This is confirmed by a study by Peterson of a group of patients with severe diabetes previously treated and instructed at The Mayo Clinic. The majority of the patients investigated had found it possible to carry on their former programs of work and recreation. Three out of every four of them had been able to adjust their lives, felt no handicap because of the imposed regimen and had made satisfactory emotional adjustments to the changes necessary. Four out of every five had emotional attitudes that were positive and healthy. Many of the failures in adjustment were caused by factors other than diabetes. Miss Peterson concluded: "The majority of patients with severe diabetes have become useful and happy people, taking their places with their associates, and asking neither sympathy nor special consideration. As a group they are proving that diabetes as a chronic disorder need be no handicap, and that personality and character are the factors determining the effectiveness of treatment."

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CHAPTER V

REQUIREMENTS FOR EFFECTIVE THERAPY IN DIABETES

The treatment of diabetes formerly was so complicated that the average physician came to believe that only a specialist could undertake it successfully. Fortunately more effective and simpler methods are now available, so that with a few principles held in mind, and with a minimum of equipment, the general practitioner, in most cases, ought to be able to obtain as satisfactory results as the specialist.

The requirements for effective therapy without which the prognosis and course of diabetes are affected unfavorably include: (1) some knowledge of the subject on the part of physicians—more knowledge than many now possess, (2) a modicum of laboratory equipment, (3) careful instruction of patients, (4) an understanding of the principles of general nutrition, and (5) a certain amount of wisdom to temper the whole, so that treatment may be adjusted as required to meet special needs of the individual. As Naunyn once stated: "Der Verlauf der Krankheit ist so verschieden wie denkbar."[1] Although the therapeutic procedure which is to be described in this and later chapters will be found suitable for the majority of patients, modifications of it to meet individual variations are necessary.

LABORATORY EQUIPMENT

Very little equipment is required to treat diabetes successfully. Facilities always must be at hand for performing qualitative tests for the presence in the urine of dextrose and acetone or diacetic acid, and it is desirable for the physician to be familiar with one reliable method for the quantitative determination of urinary dextrose.[2] In former years, when chronic acidosis needed to be dealt with so frequently, quantitative determinations of the am-

[1] "The course of diabetes is as variable as can be thought."

[2] The new Sheftel quantitative test for sugar in the urine, as further simplified by Rhodehamel, Rose and Chen, is so convenient and easy that persons unacquainted with it can obtain approximate results, and with training can secure figures correct to about 0.1 per cent. The time required to perform this test does

monia in the urine were considered indispensable. Today, in cases in which treatment has been given, chronic acidosis no longer is a problem and, as a rough measure of the degree of acidosis in cases of acute acidosis, the carbon dioxide combining power of the plasma is reliable. Facilities for measuring carbon dioxide combining power of the plasma and the concentration of the sugar (dextrose) in the blood should be a part of the office equipment of every general practitioner. While these determinations frequently can be dispensed with by the experienced physician, both examinations are of immense assistance in the treatment of acidosis, and the latter is needed in the original diagnosis of diabetes and in distinguishing it from forms of benign melituria[3]

The method for determining the carbon dioxide combining power of the plasma is that described by Van Slyke. It involves the use of a special pipet in which oxalated blood plasma first is exposed to a standard atmosphere of carbon dioxide and then to sulfuric acid. The carbon dioxide which thereby is released is measured on a graduated scale. A pipet with the scale bearing portion 2 5 times the standard length promotes accuracy in reading the very low values encountered in diabetic acidosis.[4]

Methods for determining the sugar content of the blood make use either of blood drawn from the vein (macromethods) or of capillary blood (micromethods). The latter methods are particularly advantageous in cases in which the patients are children

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not exceed five minutes The equipment necessary (obtainable from the Eli Lilly Company, Indianapolis) is contained in a small bakelite case A tablet dissolved in the urine provides the reagents, heat is effected by burning a tablet of methenamine and the resulting colors are compared to those of color charts and read off directly in per cent of dextrose.

[3] "The physician who has a laboratory so neat and modern that he is glad to take his patient into it scores much in reputation . The comparison between the outlay which the surgeon is willing to make for the conduct of his practice with that of the physician is most unfavorable to the latter The surgeon almost invariably takes pride in his equipment, purchasing new apparatus and discarding old with lavish hand The physician seldom expends the fraction of this outlay in the development of a laboratory This should be entirely different The physician should take as much pride in a well-equipped laboratory as the surgeon in his instrument case" (Joslin)

[4] Measurement of the carbon dioxide content of the plasma necessitates a manometric gas apparatus and blood drawn under oil It gives additional and more precise information, but is not necessary for routine clinical work Measurement of the hydrogen ion concentration of the blood by electrometric or other methods provides additional information, but this too can be dispensed with for clinical purposes

as well as in cases of acidosis in which the veins are collapsed. These methods also are advantageous when it is desirable to obtain a series of blood sugar determinations at short intervals. They are described in the manuals of biological chemistry.[5] Capillary blood is obtained by puncture of the skin of an ear lobe, a finger or, in the case of infants, the heel of the foot. When it is used values slightly higher (1 to 3 mg. per 100 c.c.) than those obtained with venous blood usually are found.

Methods for determining the lipoids of the blood (cholesterol, cholesterol esters, lecithin, fatty acids and total lipoids), which frequently are grossly elevated in diabetic acidosis and sometimes are higher than normal in the absence of acidosis, are not simplified enough to make them available for clinical routine. Other examinations which frequently are made include the determination of the value for the total nitrogen and special fractions of nitrogen in the urine, the determination of the value for the nonprotein nitrogen and its fractions in the blood, and the quantitative analysis of carotene and various electrolytes in the blood. None of these tests, however, is indispensable in routine clinical procedure.

OTHER EQUIPMENT

Physicians always should be prepared to treat diabetic acidosis and severe attacks of hypoglycemia without loss of time. Therefore, they should have on hand, preferably in the professional satchel, the supplies necessary for both diagnosis and early treatment of these conditions. The supplies include:

1. Insulin, both unmodified and protamine-zinc insulin.
2. Hypodermic syringe and needles
3. At least one ampule of 500 c.c. of sterile physiologic solution of sodium chloride.
4. Ampules of sterile solution of dextrose (50 per cent) for intravenous injection in cases of hypoglycemia
5. Ampules of solution of epinephrine (1 1000), principally for the same purpose.

[5] Blood plasma contains other reducing substances than dextrose Among [illegible] In consequence the Folin method for deter- [illegible] mg per 100 c.c. even [illegible] to provide the true [illegible] hands, combines the [illegible] ns of the blood with the Hagedorn and Jensen technic for determination of the reducing substance of the filtrate

6. Benedict's solution, test tubes and alcohol lamp (or tablets of methenamine) for testing for sugar on the spot*
7. Solution of ferric chloride for the Gerhardt test for diacetic acid, or crystals of sodium nitroprusside and solution of ammonia for the Legal test for acetone.
8. A stomach tube.

THE INSTRUCTION OF PATIENTS

In the long run what the diabetic patient can be taught to do for himself will count for more than what is done for him. It helps relatively little to save a life by successful treatment of an attack of severe acidosis, unless before the patient be dismissed he has learned how to live healthily and happily. First and foremost, therefore, among the essentials for successful treatment is this instruction of the patient in what he has to do for himself, or in the case of a child, instruction of the parents This course of training must be thorough and, to provide for it, systematic arrangements must be made. If the physician does not have the time to educate these people himself, or lacks the training necessary, it is inexcusable for him to fail to provide otherwise for what needs to be done.

For the instruction of patients, one or another of the many manuals written for the patient or, as in the case of my "Primer," for the patient and physician, is satisfactory. These contain directions and charts for preparing diet prescriptions, menus and recipes which provide predetermined amounts of foods for diabetic diets, and explicit directions about the use of insulin and the avoidance of complications.

In my "Primer" are included 127 questions which patients attending the diabetic school at The Mayo Clinic are required, without prompting, to answer before they are willingly dismissed The number of questions gives some idea of how much a diabetic must know. The dietitians, to be found today in almost all hospitals, or nurses with special experience, can be recruited for this important teaching. Dispensaries usually provide diabetic schools for the indigent, the wealthy can command the services of specialists, but as in so many other situations, the lower middle class

*When symptoms suggest diabetic acidosis, postponing of testing of the urine until the physician returns to his office is unjustifiable The outfit in a bakelite case described in footnote 2 (p 72) is very convenient for carrying in the professional satchel

is likely to suffer neglect. The opportunity which this class offers for lifesaving work by the medical profession is enormous.[7]

Patients must be taught how and when to test the urine. In some cases of emotionally unstable individuals too frequent testing is to be discouraged, or some other member of the family should undertake the duty. But unless the test can be performed as frequently as necessary and with no more ceremony than can be avoided, the progress of the disease cannot be controlled effectively[8] The drugstore laboratory is likely not to be reliable, and testing at least once a day, and usually twice, would involve too great an expense to the patient, if demanded of physicians. Furthermore, if the test is to serve as a guide for the amount of insulin to be taken it needs to be done at specific times of the day and the result must be known at once. Benedict's qualitative test is all that is necessary, and the patient readily can learn how to perform it. It is very important to prove the reliability of each new supply of Benedict's solution. Once in a while the druggist omits some ingredient and false reactions result In my experience insensitive Benedict's solution has lulled patients into a false sense of security, with an attack of acidosis resulting. Also, it is important for the patient to know that urine for testing should be freshly secreted by the kidneys, the bladder being emptied thirty minutes or an hour before the collection for testing is made; otherwise, the specimen may show sugar long after the blood sugar has fallen to a normal level, or vice versa, and give deceptive information as to whether or not the dose of insulin is greater or smaller than it should be.

It is necessary for the patient to be able to perform the Legal test (nitroprusside) for acetone, or the Gerhardt test (ferric chlor-

[7] "There is nearly enough knowledge today for the adequate treatment of diabetes, but it needs more general and more intense application and the development in the patient of a deeper sense of his own responsibility for his care. Coma should be abolished, gangrene halved, tuberculosis prevented, pregnancy in suitable cases made safe, ... the ultimate goal being the avoidance of death in any way due to the disease" (Joslin)

[8] "Patients weary of testing the urine, but any modern patient knows that without urinary examinations a diabetic cannot secure the best results. Only under very exceptional circumstances should they be allowed to omit making the test. A daily negative Benedict reaction gives confidence and, on the other hand, in the presence of danger, it is never wise to follow the habits of the ostrich. Advice to omit tests because they affect the psychology of the patient hastens the approach of death Rarely there is an exception to this rule" (Joslin)

ide), especially if a method of treatment is adopted which is popular in Europe. In this method glycosuria is permitted and only enough insulin is used to prevent ketosis.

Instruction about insulin and its use must be provided and prejudice against it, and in many cases fear of the hypodermic injection, must be overcome. The credulity that some people have about oral substitutes for insulin is a source of danger. I usually emphasize the importance of accuracy of dosage and that the necessary precision can be insured only by means of the hypodermic injection. New patients frequently harbor the belief that insulin, if once used, can never be discontinued thereafter. They think of it as a habit-forming drug, and the physician must explain that this is untrue and that the probability of being able to do without insulin at some later time is increased by taking insulin when it is needed. It is very important and very difficult to make clear that the unit of insulin is a standard measure and that the different concentrations of insulin, U-20, U-40, and so forth represent solutions with different concentrations of insulin and are not insulins of different strengths, therefore, that x units of U-20, although differing in volume, represents the same dose as x units of U-40, or any other concentration of insulin. All of these topics must receive adequate attention in the course of the patient's instruction.

It is very important to train the patient thoroughly in the technic of hypodermic injection, with special emphasis on the need for sterility (see p 87). The areas of the skin suitable as sites for injection must be pointed out and the patient given implicit directions about filling his syringe, preparing the site and making the injection In our clinic he also is trained to adjust the doses both of unmodified and of protamine zinc insulin to his fluctuating requirements [*]

The insulin reaction is another subject with which patients using insulin must be thoroughly familiarized. Unless they are pr[illegible]

the [illegible]
fact that a large proportion of our patients live at a great dis[illegible] by the many of them could not afford the frequent visits to physician[illegible] because would be necessitated Also, regretful as I am to mention it, [illegible] otherwise until recently, have been less dependable in the matter of adjus[illegible] physicians to the requirement than the well-trained patient. [illegible] of insul[illegible]

how to combat them they cannot avoid serious attacks of hypoglycemia For similar reasons the patient must be acquainted with the early symptoms of acidosis; he must know that acute emergencies are likely to provoke this serious complication and that delay in calling a physician may invite disaster.

Older patients must learn about the hygiene of the feet and must be instructed in those measures which will protect them from gangrene, ulcer and neuritis. This is of extreme importance. Gangrene today occupies a pre-eminent position as a cause of death of patients with diabetes.

The prescription of the diet, to my mind, should be left exclusively to the physician and no changes should be permitted without the physician's knowledge, except in cases of illness when one of several previously arranged emergency diets is to be substituted The plan now in use in the clinic is to prescribe the diet in the form of standard menus and to instruct the patient how to choose substitutes for the various items in the menus. We no longer teach calories or ask patients to learn how to construct menus from a prescribed number of grams of the various food factors. We do believe that weighing the food is desirable for the first six months of management, or until the patient has thoroughly trained himself to measure or estimate portions of food with accuracy. It requires much experience to "eat quantitatively" without using food scales.[10]

NUTRITIONAL PRINCIPLES

I cannot close this section on the requirements for effective therapy without referring again to the importance of knowledge of the principles of nutrition. There is no valid reason to believe that the insulin treated diabetic requires fewer calories than the nondiabetic, or less calcium or less protein or less iron, and some evidence supports the assumption that his need for certain of the vitamins—especially some of the elements of the vitamin B complex—is even greater than normal.

[10] The food scales should be well made Those provided by John Chatillon and Sons, [illegible]
North Ad. [illegible]
able and [illegible]
stituted for the scale pan The dials of these scales are graduated in grams, [illegible] also is advantageous inasmuch as the 100 gram portion so frequently is employed in food tables, and what calculating is necessary in making substitutions is simplified by employing the metric system

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CHAPTER VI

SUBSTITUTION THERAPY: INSULIN AND PROTAMINE-ZINC INSULIN

The theory underlying the administration of insulin is that of substitution therapy, whereby compensation can be obtained for deficiency of the pancreatic islands. With due regard to variations in the diet, insulin is injected to provide for the utilization of what dextrose enters the circulation from the liver (endogenous supply) or by absorption from the intestines (exogenous supply). Dosage depends both on the degree of pancreatic deficiency and the intensity of activity of mechanisms opposed to insulin. In the milder forms of diabetes, satisfactory control of the metabolic processes usually can be obtained by limiting the exogenous supply and no insulin is needed, whereas with increasing degrees of insular insufficiency or with increased activity of contra-insular mechanisms insulin must be given in increasing doses.

The story of the discovery of insulin by Banting, Best and their associates, as recounted by Banting, is as follows:

"A very great deal of research had been done on the pancreas previous to 1920 It was known that there were two types of cells. One group, called acinous cells, produce powerful enzymes which are poured into the intestine for the digestion of food. These cells produce the external secretion. The other cells are fewer in number and occur in groups and are called the 'Islands of Langerhans' These are the cells which produce the internal secretion

"It was known that the extirpation of the pancreas resulted in diabetes It was also known that if the pancreatic duct was tied there was an atrophy of all the glandular cells which produce the external secretions, but the animal did not become diabetic Many investigators had tried to make active extracts of the pancreas that would be of value in the treatment of diabetes

"The original hypothesis on which the work on insulin was based was that the enzymes of the cells of external secretion destroyed the active antidiabetic product of the cells of internal secretion Our whole effort was directed, therefore, to eliminating the destroying substances. We first ligated the pancreatic ducts in a number of dogs, waited some weeks for the acinous cells to degenerate, then removed and extracted the remaining cells This extract was tested on a dog that had been rendered diabetic by removal of its pancreas It was found that extracts made in this way contained an antidiabetic substance, since they improved the clinical condition of the animal and decreased the amount of sugar in the blood and urine. Active extracts

eas were also made by exhausting the glands of external secretion ...ting rid of their destroying enzymes.

...then found that an extract made from the pancreas of foetal ...der 4 months' development contained a powerful anti-diabetic ...Finally we found a chemical means of extracting the active anti... ...stance from the whole adult pancreas of the abattoir animals ...roduction of a purified product then became the problem of the ... Best, Collip, Shaffer, of St Louis, and Clowes, of the Eli Lilly ...ust be given the credit for the early work on the purification ... experiments on animals it was found that the physiological de... caused by the removal of the pancreas could be corrected by the ...on of insulin It was proved that the increase of sugar in the

...rnal secretion of the pancreas and that its administration would ...ymptoms of diabetes"

REQUIREMENT FOR INSULIN

...ases of diabetes, both mild and severe, the requirement ... is significantly affected by factors other than the func... ...e islands of Langerhans First among these is the rate ... of dextrose from food. Attempts have been made to ...atios between injected insulin and supply of dextrose ...s differ widely with the dose of insulin and with that ...e, also with various known and unknown clinical devia... the normal. Nevertheless, they possess a considerable ...ignificance, and with isocaloric diets one is reasonably ...uming in most cases that an increase in the required ...l result whenever a change is made from a diet provid... ...igar-forming material to one larger in such materials ...1924).

...equirement for insulin also is greatly affected by the ...bolism, with isosaccharic diets the one higher in calories ...lemand for more insulin and vice versa

...linical disturbances which affect the requirement for ...e those which were considered in Chapter IV under ...fluencing sensitivity to insulin. Insensitivity, as was ...ends on the intensity of action of the endocrine antago... ...sulin—pituitary, adrenal, thyroid—on the existence or ...stence of acidosis, on infection, on abnormalities of the ... on the degree of irritability of the vegetative nervous

system. The extreme degrees of insensitivity—so-called insulin resistance—have not been explained; in them enormous doses of insulin become necessary.

INSULIN

The unit of insulin.—Insulin is a protein with a molecular weight of 35,100. This molecular weight and the sedimentation constant, molar friction constant and molecular radius of insulin are, within the limits of error, identical with the corresponding constants for egg-albumen and Bence-Jones protein (Sjögren and Svedberg). At least nine amino-acids have been separated from insulin, among them cystine, tyrosine, arginine, histidine, lysine and leucine. The free substance has not been obtained in crystalline form; the hydrochloride likewise has not been crystallized, but salts of insulin with zinc, cadmium and other metals have been crystallized. Abel and his associates were the first to do this. Such crystalline preparations have a potency of approximately 22 units per milligram. By definition of the Standards Commission of the League of Nations in 1923, the unit of insulin was that amount of the active principle of the insular cells of the pancreas required to reduce the blood sugar of a healthy rabbit weighing 2 kg. which previously had been fasted for twenty-four hours, from its normal level of approximately 0.120 gm. per 100 c.c. to 0.045 gm. per 100 c.c. Later the potency of the preparation was tested by comparison with a standard preparation of insulin hydrochloride in a dry, powdered form, prepared by Dudley of the National Institute for Medical Research, London, England. A crystalline preparation now has been substituted for the amorphous standard. There is no change in the size of the unit and the lowering of blood sugar in rabbits or the production of convulsions in mice are the effects of the hormone that are depended on for the comparison of unknown with standard products (Best and Taylor).

Commercial insulin.—Commercial insulin is available in several forms. That originally provided was a buffered solution in water of insulin hydrochloride. It now is commonly spoken of as "regular insulin." Better terms would be "solution of unmodified insulin" or "solution of insulin hydrochloride." The solution of crystalline insulin commercially available contains only the minute amounts of zinc necessary for crystallization and dif-

fers inconspicuously in activity from solution of insulin hydrochloride. In what follows the term "unmodified insulin" will be used to denote either "regular insulin" or "solution of crystalline insulin"

Protamine-zinc insulin, first made available in 1937, is a chemical combination of insulin with protamine and added zinc. At the *p*H of the tissue fluids it is insoluble. Thus, its absorption is delayed and its activity prolonged The amount of zinc contained is 1 mg per 500 units Hagedorn, of Copenhagen, Denmark, is responsible for discovering this means of prolonging the activity of insulin. Protamine is a polypeptide obtained from the sperm of rainbow trout, mackerel or salmon. Scott and Fisher, of Toronto, added the zinc, after noting that protamine had little effect on the rate of absorption of perfectly amorphous insulin hydrochloride, but that when zinc was added the characteristic slowing occurred The original Danish protamine insulin presumably contained sufficient zinc or other metal as an impurity to produce this effect.

All forms of commercial insulin are dispensed in 10 c c rubber-capped vials Solution of unmodified insulin (regular insulin) is obtainable in various concentrations· "U-20" has 20 units to the cubic centimeter, "U-40," 40 units to the cubic centimeter; and so on up. The uniform system of colored labels adopted by certain manufacturers is as follows

Yellow label	"U-20"	contains 20 units in each c c
Red label	"U-40"	contains 40 units in each c c.
Green label	*"U-80"*	*contains 80 units in each c c.*

Protamine-zinc insulin at present is provided in two strengths "U-40" and "U-80" Both have a white label with red lettering

Choice of insulin.—Almost all patients who require insulin and now are under therapeutic direction from The Mayo Clinic are receiving protamine-zinc insulin. However, in the large majority of cases it is not used alone, but is combined with one or two supplementary doses daily of unmodified insulin. Our reason for using protamine-zinc insulin is not so much that it makes necessary fewer daily injections, or that a saving in the unitage required usually is observed, although both of these are good reasons; the principal advantage of protamine-zinc insulin is the continuity of insulin activity easily obtained with it and difficult

to secure with shorter-acting insulins, unless more frequent injections are made than is convenient or practical.[1] I have demonstrated experimentally that continuity of insulin activity is necessary to prevent the occurrence at intervals of periods of protein wastage associated with ketosis (Wilder, 1937). Doses of protamine-zinc insulin inadequate in severe cases completely to control glycosuria provide protection for the tissue protein and thus make possible satisfactory treatment with less rigid control of glycosuria than formerly was required. The conclusion is supported by the response of a group of juvenile patients formerly difficult to treat successfully. In some of these cases the control of glycosuria with protamine-zinc insulin has been no more satisfactory than before, but the periodic azoturia and ketonuria formerly encountered have been missing and growth and development have been more satisfactory.[2] Improved sense of well-being also has been observed by patients with less severe diabetes, whose glycosuria formerly had been well controlled with no more than two or three doses daily of unmodified insulin. This is less easily explained—*it may be partly imaginary, but the report is heard frequently* enough to be impressive.

Measuring doses of insulin.—Patients and others frequently are confused when it comes to measuring prescribed doses of insulin. *It is difficult in their instruction to make it clear that a unit of insulin is a unit, whether it is taken from a* "U-20" vial or a "U-80" vial, and confusion is likely to occur when syringes are used which are graduated in units rather than in fractions of *a cubic centimeter. For this reason I prefer to prescribe a* 1 c c.

[1] The authoritative opinion now current supports this conclusion, although not all writers are agreed A comment of Whitehill and Harrop is that patients who are lax in the management of their diets do badly on protamine-zinc insulin, and that in such cases unmodified insulin is safer, and on the whole, more satisfactory. Also, in cases in which diarrhea is a complication and in which absorption from the bowel is variable, Whitehill and Harrop expressed the opinion that protamine-zinc insulin is unsafe. Sherrill and Cope, while admitting that protamine-zinc insulin represents a distinct advance in diabetic treatment, questioned whether any particular advantage would be gained from it in cases in which previously an essentially normal balance could be maintained with unmodified insulin

[2] *Lawrence and Archer have made a similar comment*: "A striking feature is complete absence of ketosis throughout the twenty-four hours, much more complete than we have ever obtained by three doses of soluble insulin in severe cases of diabetes Even during the period of hyperglycaemia and glycosuria after a meal there is no recurrence of ketonuria, as judged by the sensitive nitroprusside test It appears that the worst defect of diabetics, the endogenous production of new sugar and acetone bodies, is incomparably *better controlled than ever before*."

syringe marked only with divisions of 1 c.c.[3] I then can explain that the syringe, when filled to the 1 c.c. mark, contains the number of units indicated by the label of the vial from which the insulin is drawn—20 units in the case of a "U-20" vial, 40 units in that of a "U-40" vial, and so on, and that smaller doses will be fractions of these totals (Fig. 7).

Stability of insulin.—The commercial preparations of insulin and those of protamine-zinc insulin are astonishingly stable, retaining their original potency for twelve months or more, providing the container has not been entered for withdrawal of any

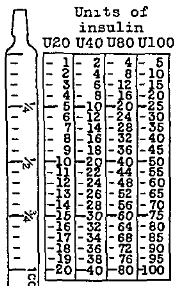


Fig 7—Syringe for injecting insulin (see footnote 3). Chart devised by a former assistant, Dr Arnoldus Goudsmit, Jr

part of its contents The activity of insulin remaining in a partly emptied vial for more than a month, or at most two months, should not be depended on It is wise to keep insulin at temperatures below 90° F Freezing also is to be avoided, as it causes some loss of strength, and in the case of protamine-zinc insulin, slight clumping. More strength is lost if, after freezing, thawing occurs rapidly. Frozen insulin should be allowed to thaw gradually at room temperature.

[3] The Becton Dickinson Company, Rutherford, N. J., has prepared such a syringe. It is their Syringe no 60, the Wilder syringe for insulin

METHODS OF ADMINISTERING INSULIN

Insulin is inactivated by the enzymes of the stomach and intestine; thus its administration parenterally is obligatory. Intravenous administration is resorted to in emergencies when an immediate effect is desired, as in the initial treatment of coma, but the usual method is by hypodermic injection. The site chosen for injection is important. Proximity to joints must be avoided, and places where the skin moves freely over the underlying muscles are preferred. The most suitable places are the thighs, the upper arms, the abdomen and the buttocks.[4]

Repeatedly changing the site of injection is of great importance, to avoid induration of tissue and insulin atrophy of fat Children are the worst offenders in neglecting this admonition. They quickly learn that a site loses its sensitivity after multiple injections into it, and then dislike changing to another site. Failure to change the site of injection frequently leads to still another complication. After the subcutaneous tissue becomes indurated absorption is retarded and later, when insulin is given in some other place, a quicker and more intense effect than is anticipated is obtained.

Minimal soreness follows an injection of insulin when the point of the needle comes to rest beneath the derma, without penetration of the connective tissue sheath of the underlying muscle; that is, in the subcutaneous fatty tissue, the panniculus adiposus. To effect a satisfactory injection it is best—as Dr. Wood-

[4] Only unmodified insulin is suitable for intravenous injection Methods of administration of insulin, such as rectal, vaginal and nasal, have failed in clinical usefulness, chiefly because effects have been slight and variable Major's results with insulin mixed with diethyleneglycol monoethyl ether for rubbing into the skin have not been sufficiently satisfactory to justify their adoption in practice A suggestive observation is that made by Blotner (1936), namely, that the inactivating effect on insulin of gastric and duodenal extracts is prevented in vitro if the

ciates. In Murlin's experiments insulin was placed in Thiry-Vella loops of jejunum of dogs and absorption was judged by reduction of the concentration of blood sugar In 61 per cent of trials using four dogs with normal pancreases, and in 73 per cent of trials with two depancreatized dogs, the results were positive The addition to the insulin of hexylresorcinol and other alkyl resorcinols and sodium bicarbonate favored its absorption; in other experiments a mixture of hexylresorcinol, sodium bicarbonate and insulin given orally to normal dogs caused a reduction in blood sugar of 0 02 gm per 100 c c in about half of several experiments Observations on patients with diabetes were not reported

yatt has taught me—to insert the needle at right angles to the fold of skin which is pulled up to receive the insulin (Fig 8). By this means, if the point of the needle has been embedded in the corium, it is freed when, the fold being released, the skin resumes its normal position (Fig 9). The most satisfactory needle in our experience is a ½ inch-25 gauge Yale rustless steel hypodermic needle.

The danger of infection in the site of injections of insulin must be relatively slight, to judge from the few accidents of this nature that have been encountered. Nevertheless, precautions should be observed and patients carefully instructed therein. The safest procedure for their unskilled hands is to keep syringe and needle continuously in alcohol. Grain alcohol, 70 per cent, is bacteriostatic, and needles and syringes which are immersed in such alcohol for the intervals of many hours between injections are reasonably sterilized. Unskillful patients frequently will touch the needle blade when making the injections but, if the equipment has just been removed from its alcohol bath, and needle and syringe are still wet with alcohol, the danger of contamination by touching is diminished. As evidence of the safety of this procedure, I can say that we have used this technic on our hospital service since the introduction of insulin in 1922, that in the intervening years no fewer than 150,000 injections of insulin must have been made, and that to my knowledge no infection has occurred. Nor have I learned that any patient instructed by us in this procedure has infected himself.

A convenient receptacle for the insulin syringe is a long, thick-walled test tube with a cork stopper. The tube is half filled with 70 per cent alcohol, or alcohol reinforced with 1 part of phenol to the 100,[8] and a small wad of cotton is placed in the bottom. A piece of thread should be tied to the syringe. The

[8] Sterilization of the needle and syringe with alcohol is the safest method for patients to follow. It also is entirely effective, especially if the alcohol used for the purpose is 70 per cent ethyl alcohol, reinforced with 1 part of phenol to the 100 and if the insulin syringe and needle are kept continuously immersed in it. Other medicated and denatured alcohols contain substances injurious to either the needles or the insulin. A convenient pocket case of bakelite is manufactured by the Becton Dickinson Company, Rutherford N J. A Wilder syringe fits into a cylindrical, water tight holder containing alcohol, and receptacles are provided for keeping needles in alcohol, for a small amount of cotton and for one bottle of insulin. The case is labeled "B D Diabetic Outfit with Syringe Number 60."

syringe with needle attached is lowered into the alcohol; the end of the thread is allowed to emerge from the neck and is fastened there by the cork. Kept in this way syringe and needle are always sterile and ready for use. Boiling to sterilize is time consuming and may crack the syringe. When the patient is through using it, the syringe should be rinsed with alcohol and replaced in the tube. A block of wood about 3 inches (7 6 cm) square and 1½ inches (3 8 cm.) thick, with a hole in the center of a size to admit the end of the test tube, serves as a convenient holder.

The patient is instructed as follows:

Directions for injecting insulin.—When preparing to take insulin empty the syringe and needle of all alcohol by pulling the plunger back and forth several times. Wipe the top of the bottle containing insulin with a piece of cotton wet with alcohol Fill the syringe with air by pulling the plunger back, then push the needle through the clean rubber cap of the bottle. Force the air contained in the syringe into the bottle, then fill the syringe with the required amount of insulin, taking care to avoid air-bubbles.

Before withdrawing protamine-zinc insulin the bottle must be inverted several times until its contents are thoroughly mixed Avoid violent shaking to prevent undesirable foaming. A satisfactory mixture is evidenced by a uniform milky appearance. After mixing withdraw the dose required and inject this without delay; otherwise the protamine-zinc insulin will settle out and the dose will be diminished. The activity is in the insoluble suspension, not in the liquid. If settling occurs within the syringe remix by inverting the syringe several times before injecting

Wash the skin where the insulin is to be injected with cotton wet with alcohol, pick up a fold of skin between thumb and forefinger and insert the needle into the side of this fold, as shown in Figures 8 and 9 (see p. 86). Release the skin; then push home the plunger of the syringe. Firmly hold the piece of cotton previously used for a sponge over the point of injection and withdraw the needle. Massage gently with the piece of cotton, but do not change its position. Massage, but do not rub.

We have not been able to determine that the minute amounts of pure grain alcohol introduced into the insulin vial by this

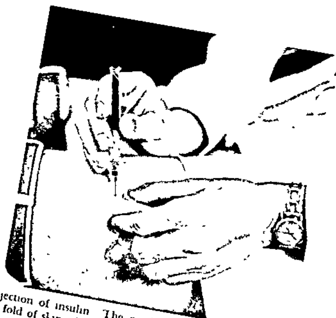


Fig 8 – Injection of insulin The needle is inserted at right angles to the fold of skin which is pulled up to receive the insulin

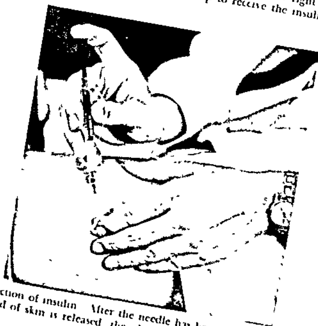


Fig 9 – Injection of insulin After the needle has been inserted (Fig 8) the fold of skin is released the plunger is then pressed home

technic affect the activity of the insulin. In the hospital we add 10 per cent of glycerol and 1 per cent of phenol to our 70 per cent "insulin alcohol" to reinforce its bacteriostatic potency and diminish potability. Propyl alcohol also may be used. Other medicated or denatured alcohols should not be used.

TIMING AND ADJUSTMENT OF DOSES OF INSULIN

Insulin prescriptions.—Orders for giving insulin are written as follows; patients and nurses are instructed accordingly: 20 - 5 - 10 indicates that three doses only are considered, one to be given before each of the three major meals, and in this example, 20 units before breakfast, 5 units before lunch and 10 units before supper. If a fourth figure is added, for example: 20 - 5 - 10 - 3, it means that the first three doses are to be given before the meals, and the fourth (in the example, 3 units) at bedtime.

Plain figures, as in the examples cited, are used for unmodified insulin. For doses of protamine-zinc insulin the letter "P" is added. For example 30P/10 - 0 - 10 would stand for 30 units of protamine-zinc insulin, together with 10 units of unmodified insulin, before breakfast, no insulin before lunch and 10 units of unmodified insulin before supper.*

Timing unmodified insulin.—Unmodified insulin should be injected, as a rule, not more than fifteen minutes before meals. When it is used alone two, three or four doses usually are given daily; the fourth dose is a small one administered without food at bedtime.

Timing protamine-zinc insulin.—To judge from the blood sugar time curves of fasting patients, the action of a given dose of protamine-zinc insulin begins without delay and continues at a low uniform intensity until the values for blood sugar reach a minimal level. Thereafter it keeps the values at this level for forty-eight hours or more. Administration of food with protamine-zinc insulin shortens the duration of this action. Even when food is taken, however, some effect persists for many more than

*To indicate the use of other forms of insulin, additional initials may be necessary. For instance, we recently have been investigating the effectiveness of a soluble form of protamine zinc insulin. In prescriptions for it the figure indicating the number of units is followed by the letters "P.s." There seems to be no further need for separate symbols for protamine insulin and protamine zinc insulin, since use of protamine insulin without added zinc has been replaced entirely by protamine zinc insulin.

twenty-four hours These observations and other evidence indicate to me that the maximal tolerable dose of protamine-zinc insulin does not exceed what is necessary to maintain the urine sugar free during the fasting hours of the night This, as Himsworth has stated, should be the objective and larger doses should not be used. To expect protamine-zinc insulin in severe cases to inhibit the rises in sugar content of the blood after meals, and to give large enough doses to prevent such rises will lead inevitably to reactions during the fasting hours of the night.

The administration of protamine-zinc insulin in one dose daily before breakfast, as has been advocated (Wilder, April, 1936), is now widely adopted By this technic the test of the urine passed before breakfast becomes a very accurate gauge of the tolerable dose When this specimen of urine contains sugar, the patient knows that the dose does not meet the rate of endogenous supply of sugar. Therefore it can be increased with safety. On the other hand, if the morning urine is sugar free, the dose evidently is large enough, and the next question is, is it too large. A reaction occurring in the early morning hours of the night is evidence of excess, but it is not wise to wait for reactions. Our rule is to reduce the dose when the morning urine is sugar free

Adjusting the doses of insulin—In cases in which there has been no previous treatment, and in which acidosis is present, heroic treatment is indicated, as will be described in Chapter X. In the absence of acidosis a suitable diet is prescribed and the effect of this is observed for four days. During this period twenty-four hour collections of urine are obtained and analyzed quantitatively for dextrose The amount contained in the specimen of the fourth day serves excellently as a guide to the initial dose of insulin Whether this be unmodified insulin or protamine-zinc insulin, the total dose for the following day can safely be ⅔ of a unit for each gram of sugar found [7]

When unmodified insulin alone is to be used, the estimated dosage for twenty-four hours is then given in three equally divided doses fifteen minutes before each meal. Subsequently adjustment is made up or down, depending on the appearance of sugar in

[7] The physician who has had large experience in the treatment of diabetes is able to shorten this initial period of observation and begin injections of insulin at once, by making an experienced guess at the initial requirement.

specimens of urine collected during the hour preceding each meal and at bedtime. It frequently is possible to obtain better control with larger doses before some meals than others, or with an additional small dose given at bedtime. Twenty-four hour collections of urine and quantitative analyses are not required after the initial insulin requirement has been decided on.

When facilities are not at hand for quantitative analysis, it is well to begin treatment with small doses of unmodified insulin (5 units before each meal) and to increase these gradually day by day until the qualitative tests for sugar of single specimens of urine passed before meals and at bedtime give negative results Later, if desired, treatment can be changed to include the use of protamine-zinc insulin, as is to be described

Fractional specimens of urine, when tests of them are used as guides to administration of insulin, must be freshly excreted by the kidneys. To assure this the patient must empty the bladder not more than one hour before the specimen for analysis is collected.

Where the decision is to use protamine-zinc insulin from the beginning, the entire twenty-four hour insulin dosage decided on may be given as protamine-zinc insulin in one dose before breakfast. However, it rarely is desirable to inject more than 40 units of protamine-zinc insulin, and in most cases we now prefer to use only enough protamine-zinc insulin to provide for control during the night, adding to it what unmodified insulin is required to prevent gross glycosuria during the day This procedure is described in what follows:

Mixed insulin; one syringe—The ideal in the use of insulin is to imitate the action of the normal pancreas[*] Thus, as Lawrence and Archer suggested, probably involves (1) a small

*It rarely is possible in severe cases to obtain satisfactory control of diabetes with protamine zinc insulin alone and, in most cases, when the total dose of insulin required exceeds 20 or 30 units, injections of supplementary unmodified insulin are required to prevent gross glycosuria after meals This also has been the experience of Warvel and Shafer, and that of Himsworth The latter stated "It is only in mild cases that the new preparations may legitimately be expected to control the disease during the whole twenty four hours In cases of any severity their action should be reinforced by the administration of ordinary insulin at those times when a sudden influx of sugar from the intestine is found to overwhelm their mild action An analogy may be drawn between the use of the new insulin and a modern technique in anesthesia The protamine insulins are comparable to the basal anesthetics whose effect is both mild and prolonged ordinary insulin is comparable to the volatile anesthetic which is superimposed at times when a stronger control is required"

continuous secretion of insulin, and (2) increased secretion after meals to deal with ingested carbohydrate. *No one type of insulin can imitate both aspects satisfactorily.* Protamine-zinc insulin provides well for the small continuous supply required during the night, but if given in doses large enough also to control the glycosuria which follows meals it provokes hypoglycemia in the night. Unmodified insulin acts quickly and is best adapted to meet the requirement for more insulin activity at meal times These considerations led Lawrence and Archer and Graham to attempt the simultaneous injection in one syringe of both protamine-zinc insulin and unmodified insulin. In the mixture some of the soluble insulin may be bound by the excess of protamine present in the protamine-zinc insulin, but even so irregularities of action from day to day are no more conspicuous than when the two insulins are injected into separate sites.

We have adopted this technic with results that are very satisfactory. With it in most cases we can obtain adequate control both of postabsorptive and of postprandial glycosuria *with one injection a day, given before breakfast. It is said to be important* to draw the dose of unmodified insulin into the syringe first to avoid introducing any alkaline protamine-zinc insulin into this bottle

The directions for filling the syringe are as follows:

Using precautions with respect to sterility (see p. 88), introduce into the protamine-zinc insulin bottle an amount of air equal to the volume of the dose of protamine-zinc insulin later to be withdrawn. When doing so have the bottle down and introduce the hypodermic needle only just through the rubber stopper, thereby avoiding contact of the needle with this insulin. Next introduce air into the bottle of unmodified insulin in an amount equal in volume to the dose of unmodified insulin required. Inject this air into the bottle and withdraw the dose of unmodified insulin. Hold the syringe vertically *with the needle and bottle* up when withdrawing the needle from the bottle of unmodified insulin. Thoroughly mix the contents of the bottle of protamine-zinc insulin, and with the syringe still held vertically with the needle up, enter this bottle and withdraw the dose of protamine-zinc insulin desired. Inject the combined dose into a suitable site by the method described before (see p. 88).

The dose of each component of the mixture of protamine-zinc and unmodified insulin may need to be changed daily. Therefore, the patient must never neglect examination of the specimen of urine which he voids before breakfast and of that which he voids before supper. If it is inconvenient to do the testing before supper, arrangements can be made to save some of the urine voided at that time for testing later. A small bottle to hold enough of it for testing can be carried on the person. The bladder should be emptied not more than one hour before the specimen for analysis is collected. In other words, urine for testing must be urine recently secreted by the kidneys.

The result of the test of the urine voided before breakfast tells whether the protamine-zinc component of the mixture to be given should be increased or decreased, that of the test before supper tells whether the unmodified insulin component is to be increased or decreased. For both components changes in dosage are made in steps of 4 units, although sometimes more satisfactory results are obtained by making changes in half steps.

When the combined dose (protamine-zinc insulin and unmodified insulin) amounts to less than 30 units, insulins of U-40 strength are selected: if the combined dose exceeds 30 units U-80 insulins are preferred. On the Wilder syringe the number of gradations is 20; thus when U-40 insulin is used each gradation represents 2 units (half a step), and with U-80 insulin each gradation represents 4 units (one step).

Rules for adjustments of the doses of insulin.—Rule 1.—For the unmodified component decrease the previous dose by one step (4 units) if the urine voided *before supper* the night before gave a reaction, grade 0 or 1, not otherwise, make no change for a reaction, grade 2; increase by one step (4 units) for reactions, grade 3 or 4 (see frontispiece, colored plate).

Rule 2.—For the protamine-zinc component decrease the previous dose by one step (4 units) if the urine voided *before breakfast* gives a reaction, grade 0 or 1, not otherwise, make no change for a reaction, grade 2, increase by one step (4 units) for a reaction, grade 3 or 4

In many milder cases when these rules are followed the dose of both the unmodified and the protamine-zinc components of the insulin mixture ultimately may be stepped down to nothing,

which is undesirable *until the physician has convinced himself* that the use of insulin is without advantage. In many cases it seems to be helpful to continue administering a small dose of protamine-zinc insulin, even when the urine is sugar free. This explains the third rule which is as follows:

Rule 3.—The protamine-zinc insulin component of the mixture of insulins is not to be stepped down to less than 6 units unless the physician so orders. *This small dose can be tolerated* without danger of an insulin collapse reaction even when all specimens of the urine are sugar free.

An important exception to these three rules is contained in Rule 4:

Rule 4.—On the occurrence of a complicating infection, or other emergency, when the requirement for insulin is temporarily elevated, the dose of protamine-zinc insulin previously effective in preventing the appearance of more than traces of sugar in the morning urine is not to be increased even though a strongly positive reaction for sugar is obtained. Instead doses of unmodified insulin are to be given, according to the directions for the treatment of emergencies (see p. 201) *and the dose of protamine-zinc* insulin is continued at the previous level. This is to avoid building up a dose of protamine-zinc insulin which may be excessive as soon as the emergency has passed and because of the long duration of its action cannot quickly be diminished.

In this procedure, except when the dose of insulin *is very small* (6 units only of protamine-zinc insulin) we are encouraging the patient to permit his urine to contain traces of sugar at all times. Thus full advantage is taken of the fact demonstrated previously (Wilder, 1937) that when insulin is acting in the body, a certain degree of glycosuria is perfectly compatible with freedom *from* ketosis and stability of the tissue proteins. The reliability of this *observation has been substantiated* by a study of Tolstoi and Weber. It further is attested by the entirely satisfactory growth of diabetic children treated by this method for the last eighteen months. The great advantage of the procedure is that by *this* means insulin reactions in most cases are much more easily avoided.

I was led to adopt this procedure by the difficulty experienced in avoiding hypoglycemia and the accompanying headaches and

nausea, when enough protamine-zinc insulin used alone was given to prevent glycosuria after meals. Some authorities will disagree with the recommendation to have traces of sugar in the urine. In my opinion it is as important, for the comfort and safety of the patient, to avoid insulin reactions as to prevent other complications, and to insist on continuously sugar-free urine, when using protamine-zinc insulin, is to invite reactions. Sindoni has expressed the belief that complete control of hyperglycemia, if maintained, will delay premature arteriosclerosis, will increase resistance to infection and prolong the span of life. Richardson and Bowie even suggested that if a renal threshold is higher than 0.180 gm. per 100 c.c., examination of the urine is inadequate for the maintenance of satisfactory adjustment. This may, indeed, be true, but these statements of Sindoni are open to question, and from a practical point of view such rigid control as he and Richardson and Bowie recommended is impossible to maintain without great danger of reactions, especially when the patients are not in the hospital. It is important to discriminate between the significance of glycosuria that follows meal-taking (postprandial glycosuria) and that which occurs between midnight and breakfast (postabsorptive glycosuria). The former represents spill from exogenous supplies of sugar, and is relatively harmless, the latter is derived from stores of glycogen and by neoglucogenesis from catabolizing protein. It is the latter in all probability that predisposes to the complications attributed so commonly to glycosuria.

COMPLICATIONS FROM INSULIN

Insulin fat atrophy.—The first instances of atrophy of subcutaneous tissue of patients treated with insulin were reported by my former associate, Dr Clifford Barborka (Figs 10 and 11). In one case injections of insulin had been made in both thighs and the left arm. In the other they had been given only in the thighs. In both cases the atrophy was limited to the sites of injection. Neither patient had received proper instruction in the technic of administering insulin and one injection after another had been made into the same location. After instruction on the technic of injection no further areas of atrophy appeared. By insistence on varying the site of injection, the occurrence of these disfiguring

lesions usually can be avoided. However, they have been encountered, even with well trained patients The cause is unknown. Some type of local sensitivity of the tissues of an allergic type may be responsible. Almost all of these patients have been women.[9]

The treatment of insulin atrophy is principally a matter of prevention by the exercise of scrupulous care in the technic of the hypodermic injection. There is some advantage in using only highly concentrated insulin, such as "U-80." If the affected regions are avoided in subsequent treatment, the depressions after several months usually fill in spontaneously; occasionally they persist for years.

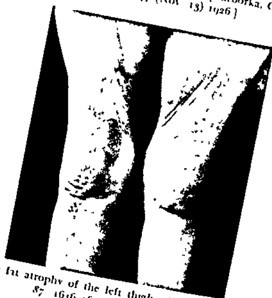
Insulin allergy.—Allergic reactions to insulin have been reported from The Mayo Clinic by Allan and Scherer. Three types were described. The first is encountered frequently. It consists only of a mild inflammation at the site of injection, which reaches its maximal severity in from twelve to twenty-four hours and subsides in from one to three days. The difficulty persists for the first few weeks of treatment; the patient then apparently becomes desensitized spontaneously.

The second type of reaction also is local but more severe The inflammation develops more quickly after each injection, lasts longer, and is associated with so much pain that remedial measures become necessary. In these cases relief sometimes can be obtained by changing to another brand of insulin. Insulin from beef pancreas frequently is tolerated, when that made from the pancreas of hogs is not, and vice versa. Solution of crystalline insulin is sometimes tolerated. Desensitization can be effected either by giving multiple, graduated doses of insulin itself, or by repeated injections of histamine, as suggested by Collens, Lerner and Fialka. In The Mayo Clinic, as described by Roth and Rynearson, we give histamine phosphate in doses of 0.05 mg twice

[9] Joslin has written that occasionally the atrophic regions are remote by several centimeters from the site of injection, and that they have even occurred in places where any connection with the local injection is excluded, but we have seen neither. No one has satisfactorily explained insulin atrophy A paper by Blotner (1938) contains a very complete review of the various theories proposed and the report of a case of local fat atrophy, which occurred in a nondiabetic th... person who took insulin for only three weeks to gain weight. The atrophy wh... was noted four or five months later remained stationary for two and ... except during a pregnancy when it appeared more marked. Sensation was ... ished over the region of the atrophy.



Fig 10—Insulin fat atrophy of the left arm [Barborka, C J J A M A 87 1616–1617 (Nov 13) 1926]



g 11—Insulin fat atrophy of the left thigh [Barborka C J J A M A. 87 1616–1617 (Nov 13) 1926]

daily for the first and second days, 0.075 mg. twice daily on the third day, and 0.1 mg. twice daily for ten additional days.

In the third type of insulin allergy, which fortunately is extremely unusual, systemic reaction occurs, manifested by diffuse urticaria, edema of mucous membranes and circulatory and gastro-intestinal disturbances. With such reactions desensitizing measures must be employed. The following illustrative case was mentioned by Allan and Scherer:

The patient, a woman aged forty-eight years, was found to have mild diabetes in October, 1923. Insulin was given for a short time in 1924 after a pelvic operation and mild local allergic irritation was encountered. In 1927 insulin again was used during a course of treatment of varicose veins. At this time the local reactions were severe and on the fourth day a general reaction occurred, consisting of diffuse urticaria, edema of the face, dyspnea and prostration. Fortunately the diabetes was mild enough to permit discontinuing the injections, but in 1930 empyema of the gallbladder necessitated cholecystectomy and after the operation intense glycosuria occurred, associated with acidosis. The carbon-dioxide combining power of the blood plasma fell to 21 per cent by volume. What was to be done? Even the minute amounts of insulin used for skin testing caused weakness, palpitation and paresthesia. A solution of crystalline insulin previously had been obtained from Dr. Scott of the University of Toronto. There was hypersensitivity to this too, but much less than that to regular insulin; thus a dilute solution could be given at short intervals, beginning with extremely minute amounts and continuing with very gradually increasing doses. Desensitization was obtained by this means and by the second day a dose adequate to control the metabolic condition could be given, so that the patient recovered.

Unfortunately this patient became so afraid of insulin from this experience that in 1939, threatened with diabetic coma, she refused to enter the hospital until three days later when she was deeply comatose. She thus received treatment tardily, and although her acidosis was controlled with insulin and other standard measures, she died. There was no allergic reaction to the insulin used at this last admission. She apparently had responded well to treatment. She had fully regained consciousness when she suddenly collapsed. Necropsy revealed dilatation of the left ventricle.

Allergy to insulin usually is not accompanied by any decrease in sensitivity to insulin, although a few cases are on record in which such allergy was thought to be responsible for insulin resistance.

A disadvantage of protamine zinc insulin has been the more frequent occurrence of dermal reactions. Usually these are limited to the site of injection. In a few cases generalized urticaria has developed after an interval of from ten to twenty days from the time of beginning the use of the preparation. There have

been no other symptoms, the skin alone being affected. The patients previously had taken unmodified insulin without difficulty and their urticaria disappeared when unmodified insulin again was used alone.

Encouraging results have been obtained in the treatment of allergy to insulin by the oral administration of histaminase. The procedure is described by Roth and Rynearson. The preparations of histaminase as yet available vary considerably in potency so that irregular results are obtained The dose is from 6 to 8 tablets a day.

Insulin edema.—When a patient with severe diabetes has received no treatment or very inadequate treatment and has become cachectic, starting of treatment, particularly with insulin, is accompanied not uncommonly by generalized edema. After the nutritional state of such a patient has improved, the edema disappears spontaneously. In extreme cases the condition may be sufficiently serious to necessitate special treatment. Withdrawal of salt from the diet and intravenous administration of solution of calcium lactate is effective. The abnormality apparently is attributable to sudden withdrawal of molecules of glucose from the circulating fluids.[10]

Insulin presbyopia.—Another effect of rapidly diminishing the concentration of dextrose in the fluids of the body, and thereby altering the water balance, is the development of transitory presbyopia Near vision is disturbed and, depending on the degree of this, as well as on the original refraction, "plus" glasses are needed to bring near objects and the printed page into focus The mechanism of this is not entirely clear, other than that the principal structure of the eye to be affected is the lens. A case was cited by Grafe in which the patient previously had suffered removal of the lens of one eye. When treatment for diabetes was begun, vision was disturbed only in the eye in which the lens remained. Apparently the lens loses its normal elasticity when an excessive concentration of sugar in the circulating fluids is rapidly reduced. This disturbance of vision is much more marked in individuals who are approaching the age of natural

[10] This temporary abnormality and what I describe next as insulin presbyopia are improperly named Both depend on rapid correction of hyperglycemia, by whatever means this is accomplished; both were recognized complications of diabetic treatment before insulin was discovered.

presbyopia and whose lenses, because of age, have already lost elasticity. It is unusual in children, but frequently young adults will state that when they look from distant to near objects the near object at first is blurred but becomes clear again in a second or two. Likewise, when they move their eyes from a near to a distant object, the distant object may look blurred at first and then promptly clear. The subject has been most extensively studied by Duke-Elder.

The disturbance is very annoying, because it occurs just at the time when the patient needs his ability to read in order to receive instruction in the care of his diabetes. Otherwise, it is not a cause for apprehension; it disappears spontaneously within two to four weeks if treatment is continued. It is important not to subject patients who are beginning treatment to refraction for glasses, or the glasses procured will be unsuitable later. However, it frequently is advantageous to arrange for the temporary use of glasses with plus 2 or plus 3 diopter lenses, to enable the patient to read what he needs to read in the course of instruction.

THE INSULIN REACTION

Depression of the blood sugar to levels well below those commonly considered physiologic represents as serious an abnormality as any that may accompany high blood sugar levels. The general subject of hypoglycemia is to receive extensive consideration in later chapters, but since overdosage of insulin is one of the most frequent causes, the subject must be given at least some attention in this place. In severe reactions the extreme collapse has been compared to a state of shock. However, the term "shock" is used inappropriately, at least from the observations of Butt and Keys.

Butt and Keys concluded that insulin shock bears no close relation to other types of shock since the total blood volume at most is altered only slightly, the principal change in the blood concentration is a result of the addition of new red cells to the active circulation. "In other conditions of shock—surgical, burn and cholera shock—the most characteristic and significant feature is a marked loss of fluid from the vascular system. In this respect 'insulin shock' is very different. It is notable that in 'insulin shock' the pulse rate shows only slight to moderate increases and

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Insulin presbyopia.—Another effect of rapidly diminishing th concentration of dextrose in the fluids of the body, and thereb altering the water balance, is the development of transitory pres byopia. Near vision is disturbed and, depending on the degre of this, as well as on the original refraction, "plus" glasses ar needed to bring near objects and the printed page into focus The mechanism of this is not entirely clear, other than that th principal structure of the eye to be affected is the lens. A case wa cited by Grafe in which the patient previously had suffered re moval of the lens of one eye. When treatment for diabetes wa *begun, vision was disturbed only in the eye in which the len* remained. Apparently the lens loses its normal elasticity when an excessive concentration of sugar in the circulating fluids is rapidly reduced. This disturbance of vision is much more marked in individuals who are approaching the age of natural

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presbyopia and whose lenses, because of age, have already lost elasticity. It is unusual in children, but frequently young adults will state that when they look from distant to near objects the near object at first is blurred but becomes clear again in a second or two. Likewise, when they move their eyes from a near to a distant object, the distant object may look blurred at first and then promptly clear. The subject has been most extensively studied by Duke-Elder.

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patients with unusually unstable blood sugar levels in treating whom everybody with experience in diabetes has run into difficulties. Woodyatt has labeled them "brittle cases." The patient passes rapidly from the condition of hyperglycemia—even with acidosis—to hypoglycemia, and back again. Such patients require most careful management and with them severe reactions can be prevented only by accepting some degree of undertreatment and carefully avoiding aglycosuric urine. The condition in some cases seems to be attributable to instability of the autonomic nervous system. The patient behaves as if the glycogen of his liver rhythmically, but not with any regularity, was released excessively and then bound too tightly.

The symptoms of insulin reactions.—In his famous "Treatment of diabetes mellitus," Joslin has a paragraph the substance of which should be held in mind by every doctor or patient concerned with diabetes. It is this:

"When a diabetic child becomes quiet, lacks interest and is unnaturally good; when an adult diabetic acts ambitionless, depressed and morose, or an elderly man or woman weak and faint, I wonder if their blood sugar has fallen below normal. Very likely they are hungry, but do not know it. If the occasion is some hours after meals, particularly if they have had an active period of exercise and I learn that they took their usual dose of insulin and, in haste, ate less than usual, I feel reasonably sure my guess is correct; and the surmise changes to certainty if I find a tremor of the hands with moisture in the palms and a few beads of sweat on the forehead. Diabetics in such a condition respond to questions like automatons, and somehow give the impression that soon they may become unconscious, or quite the reverse, become emotionally unstable."

The early symptoms of reaction to unmodified insulin are hunger, weakness, sweating, trembling and apprehension. These symptoms are less apparent when reactions follow protamine-zinc

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twenty-one adrenal [illegible]

and cortex in antagonizing insulin, since the removal of the medullary portion alone only doubled the insulin sensitivity, whereas removal of the entire gland increased it twenty-four times

the blood pressure, though more variable than normal and frequently somewhat low, never falls to the level associated with other types of shock. It would seem preferable to refer to this condition as 'insulin collapse.' Another point of differentiation between 'insulin collapse' and the shock state is in the oxygen saturation of the blood. In severe traumatic shock, for example, the venous blood frequently has a very low saturation. We have found, however, that the oxygen saturation of arm vein blood in insulin collapse is high and even approaches the arterial level. In two cases the values before insulin were 62 and 76 per cent saturation; during the height of the reaction the values were 79 and 84 per cent saturation."

Causes of insulin reaction.—Reactions from insulin occur if the blood sugar is rapidly lowered to pathologic levels, or irrespective of the speed of lowering, if a sufficiently low level is reached[11] Errors in treatment commonly responsible for reactions are the following: (1) error in filling the syringe and thus injecting more insulin than is intended, (2) irregularity in taking of food, postponement of meals, missing a meal, eating it incompletely, or vomiting part or all of the food, (3) taking more exercise than usual, (4) making repeated injections into the same site, and (5) overemphasis, especially when protamine-zinc insulin is used, of the importance of having continuously sugar-free urine.

The general nutrition of the patient affects the likelihood of reactions and their severity. Cachectic individuals are prone to develop them, partly because of inadequate reserves of hepatic glycogen, also because, in undernutrition, a small dose of insulin is more active, unit for unit Patients hypersensitive to insulin from insufficiency of the pituitary, adrenal or thyroid gland likewise must be treated carefully.[12] In addition, there is a group of

[11] Blood sugar levels as high as 0 100 gm per 100 c c. occasionally may be accompanied by symptoms Values less than 0 050 gm rarely can be tolerated without symptoms, although notable exceptions are encountered and much depends on the rate at which the level of blood sugar has fallen Thus, in a case of pituitary cachexia, the result of a chromophobe tumor of the pituitary, the blood sugar ranged around 0 040 gm per 100 c c The highest value during a long period of observation was 0 065 gm per 100 c c, the lowest 0 030, yet at no time were there any symptoms such as commonly are attributable to the syndrome of hypoglycemia (Wilder, Internat Clin., 1936). Also, as will be mentioned again, hypoglycemia induced by the slow action of protamine zinc insulin frequently is symptomless, or nearly so

[12] Swann and Fitzgerald found the smallest dose of insulin causing convulsions in twenty-three normal rats to average 2.2 units per kilogram of body weight; in

a state of acidosis to one of hypoglycemia, and the urine then is deceptive. Another index is the state of dryness of the skin and mucous membranes. They are moist in insulin reaction, unless the patient has been in acidosis recently, they are dry, usually very dry, in diabetic coma

Prognosis in insulin reaction.—No patient has died directly of an insulin reaction in our hospitals, but one patient, returning from the operating room, received accidentally an excessive dose of insulin, lost consciousness and possibly in consequence acquired fatal bronchopneumonia. An illustrative fatality occurred in a nearby town, as a result of overtreatment of diabetic acidosis in a child. We were summoned in consultation, but arrived too late The child had been given an ampule of insulin (400 units); she had regained consciousness and then lapsed again into unconsciousness, which had been mistaken for diabetic coma and had been treated with another ampule of insulin A number of other tragedies similar to the one mentioned have been only just averted The occurrence in a few cases of irreversible cerebral damage from hypoglycemia, owing to oversupply of insulin, will receive special consideration in Chapter XXIV.

Prevention of insulin reactions.—By regulating the intake of food as well as the amount of exercise, so that both will be nearly the same from day to day, and by care to avoid excessive doses of insulin, reactions can be avoided When diet and exercise vary widely from one day to the next, the difficulty of estimating correctly the amounts of insulin required becomes almost insuperable. Patients in hospital are less active than at home Quite commonly when well-regulated patients make a return visit to the hospital for re-examination, doses of insulin that at home sufficed for control prove inadequate. By the same token, when patients leave the hospital for their homes, where their activities are increased, the amounts of insulin required diminish It is important to instruct them accordingly It is important also to advise all diabetic patients that when unusual exercise is undertaken, *such as a round of golf or a game of tennis, a loaf of sugar* should be eaten before and afterward.

Patients should learn to recognize the early symptoms of reaction and when these develop to take the antidote—sugar. Hard candies which can be purchased in every drugstore in handy pack-

insulin, being replaced by drowsiness, headache, nausea, paresthesia and blurring of vision. Later symptoms, after any type of insulin, include diplopia, disorientation, loss of memory, emotional instability and finally, loss of consciousness, with or without convulsions. Before consciousness is gone, a stage of excitement may be entered, in which the patient is negativistic, hysterical, delirious or violent. A retrograde amnesia inevitably accompanies severe attacks, the patient having no recollection after recovery of anything that has happened, although he may have carried on a fairly intelligent conversation during the early stages of the attack.

Reactions to overdoses of protamine-zinc insulin when this is injected once daily usually occur in the early morning, those to unmodified insulin develop within a few hours of the time of an injection.

Diagnosis of insulin reaction.—The finding of dilated pupils, firm eyeballs, pallor, wet skin, normal or diminished respiration, normal or elevated blood pressure, normal or full and bounding pulses and overactive tendon reflexes (positive Babinski reaction) completes the picture of the hypoglycemic reaction. It is important not to mistake unconsciousness caused by insulin for diabetic coma. The consequence of giving insulin when sugar is needed may be disastrous. The distinction usually can be made by the patient's breathing. Before consciousness has been lost, the patient in insulin reaction usually behaves like a drunken sailor, resisting assistance, talking boisterously and breathing noisily and irregularly. Before coma from acidosis the patient is drowsy and slow to respond, but never resistant. His breathing is increased in depth but is regular and not noisy. After consciousness is lost in insulin coma, the breathing almost always is very light and very shallow, whereas in diabetic coma it almost always is deeper than normal, resembling the breathing of a runner at the finish of a race. The physician also may be guided by the tendon reflexes. They are overactive in insulin reaction (a positive Babinski reflex is usually obtained) and decreased in diabetic coma. The presence of sugar and even of diacetic acid in the urine must be evaluated cautiously, unless the bladder has been emptied thirty minutes or an hour before collecting the specimen for examination. Patients may pass rather quickly from

the blood sugar level. If epinephrine also is not available and the patient cannot swallow, 200 c.c. of a 20 per cent solution of corn syrup, honey or molasses, or in the absence of these, of cane sugar, may be given by stomach tube There is some doubt about the absorbability of dextrose administered rectally. Lacking facilities for any of these means of administering sugar, a teaspoonful of powdered or granulated table sugar should be placed in the mouth between the cheeks and the teeth. As it dissolves some will be inverted, yielding dextrose and fructose, and if the administration is repeated, enough dextrose ultimately will be obtained.[13]

The importance of correct diagnosis between insulin reaction and diabetic coma has been emphasized. In cases in which doubt remains it is unwise to postpone treatment, even until a report of the blood sugar can be received. Under such circumstances, I would give dextrose intravenously in a dose of 50 gm., and at the same time administer 20 units of insulin hypodermically. If necessary, I would repeat the injection of glucose an hour later and with it give another 10 units of insulin By then the diagnosis surely ought to be evident.

Reactions after protamine-zinc insulin.—The fact was mentioned that when hypoglycemia is produced very gradually, as occurs after injections of protamine-zinc insulin, it usually is not attended by the stormy symptoms characteristic of reactions to unmodified insulin. The phenomena of hypoglycemia, which have been attributed to protective mobilization of epinephrine, are less pronounced or entirely absent, and their place is taken by symptoms of cerebral origin, such as lassitude, headache, nausea and paresthesia. However, even with protamine-zinc insulin muscular exercise is likely to precipitate tremor, tachycardia and apprehension, and under any circumstances, as the reaction proceeds

[13] Cane sugar, which is valueless if given intravenously or by rectum, is hydrolyzed by saliva or gastric juices yielding dextrose and fructose Therefore, although less promptly effective than dextrose, it can be used for oral or intragastric administration Joslin has seen no harm result from solutions of sugar introduced through [illegible]

to terminate the period of unconsciousness has been to administer 500 c c of 30 per cent aqueous solution of cane sugar by means of a small stomach tube (Rosenberg and co-workers)

ages are useful for this purpose. A package of them, or sugar in one form or another, should always be carried on the person, and 10 gm. of sugar, or the equivalent in candy, should be placed in the mouth when the first symptoms appear and every half hour, or oftener, afterward so long as the symptoms persist.

Identification card.—The behavior of patients in severe insulin reaction has led, not infrequently, to the suspicion of intoxication with alcohol. For this reason it is rather important for diabetic patients using insulin to be cautious about taking alcoholic drinks. Unusual behavior, plus an alcoholic breath, may result in a visit to the police station, or worse. Furthermore, every diabetic should carry on his person an identification card, containing in essence the following information:

> I have not been drinking.
> I have diabetes, and if found unconscious or behaving abnormally, my condition probably is the result of an overdose of insulin.
> The antidote is sugar. Place sugar or candy in my mouth. If it fails to restore me in 15 minutes, call my physician or send me immediately to a hospital.
> My name is ______________
> My address is ______________
> My physician's name is ______________
> His address is ______________
> *His telephone number is* ______________

Treatment of severe insulin reactions.—The antidote for an insulin reaction is the sugar, dextrose (d-glucose). The dose required is small, even with severe reactions, and the administration of excessive amounts of sugar is to be avoided. Dextrose, 20 to 50 gm., given by vein, usually suffices to restore consciousness within a few minutes, but afterward 10 or 20 gm. administered orally at half hourly intervals until the next meal, or at least for two or three hours, may be necessary to prevent return of symptoms. Physicians, in this day of much medication with insulin, ought always to carry one or two ampules of 50 per cent solution of dextrose, so as to be prepared to meet these emergencies effectively and quickly. If such solution is not on hand, sufficient consciousness frequently can be restored so that the patient can take sugar by mouth, if 0.5 to 1.0 c.c. of 1 to 1000 solution of epinephrine is injected subcutaneously. The effect of this is to liberate dextrose from the liver, and thus temporarily to restore

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diplopia appears and the patient becomes disoriented and con-fused. Two of our patients who after injections of protamine-zinc insulin were confined to bed and fasting for many hours did not lose consciousness but, by the fifty-second hour, one of the patients became restless and irrational; his pupils dilated and the tendon reflexes were exaggerated (Wilder, 1937). In another patient who was taking only 20 units of protamine-zinc insulin daily, confusion, associated with nausea and headache, developed and the patient remained in this condition for a week before the cause of this disturbance was recognized.

Long-continued hypoglycemia such as that described is not unattended with risk. When protamine-zinc insulin was given to dogs in sufficient doses to maintain long-continued but symptom-less hypoglycemia, my colleague, Dr. Bollman, observed fatal con-vulsions. They occurred when, after hypoglycemia had been present for from fifty to sixty hours, he administered dextrose to restore the blood sugar level. The brains of these animals were peppered with petechial hemorrhages.[14] Patients fortunately are more tolerant. I have been informed of only one death attrib-utable to protamine-zinc insulin, although numerous instances of overdosage have been encountered

Treatment of severe reactions following protamine-zinc insulin must be continued for a considerably longer time than usually is necessary in reaction to unmodified insulin. Recovery is slower and relapse into a delirious or disoriented condition is likely to occur unless close supervision is maintained and the administra-tions of sugar are repeated for many hours.

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[14] Sherrill and MacKay confirmed this observation In six dogs which they made stuporous with protamine-zinc insulin, the levels of blood sugar were held for twenty-four or forty eight hours between 0 02 and 0 03 gm. per 100 c.c.; a died even after the concentration of sugar in the blood was raised to normal by giving sugar

CHAPTER VII

DIET THERAPY IN DIABETES

DIETS OF THE PAST

It is of practical as well as historical interest to review the dietary procedures which antedate the discovery of insulin. The theories on which they were based, many of them sound in principle when insulin was unavailable, may have influenced subsequent policy more than should have been permitted. This especially applies to the theory of undernutrition. For a more detailed history of diabetic diets and a bibliography which includes the references to the contributions of the earlier authors cited in the following brief account, the reader is referred to the monograph of Allen, Stillman and Fitz

Systematic dieting for diabetes began in 1796, when a surgeon general of the English army, John Rollo, attributed benefit in a case of moderate diabetes to a diet consisting almost exclusively of animal food This procedure was adhered to in principle for the next 100 years. The value of green vegetables was recognized between 1840 and 1850 by Bouchardat, who also introduced the practice of boiling vegetables and throwing away the water to diminish the quantity of starch when necessary It was Bouchardat who first devised a gluten bread This was followed by the bran bread of Prout, Pavy's almond bread and similar products much abused in later years. It was Bouchardat who originated fast days. He had noted the disappearance of glycosuria in some of his cases during the enforced deprivations of the siege of Paris

Cantani in 1880 again pushed to extremes the practice of carbohydrate privation, and allowed his patients no food at all but meat and fat. He resorted to fast days to clear the urine of sugar and was the first to insist that sugar-free urine was obtainable and desirable. Bouchardat, Cantani and others, but especially Naunyn, after 1890, came to recognize the harmfulness of an excessive meat (protein) allowance.

A number of authorities proclaimed the virtues of individual foodstuffs One of the earliest food "cures" was the "milk cure"

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was found in the urine. Allen wrote that his experiments were begun "with a view to the possibility that diabetes is a disorder of the total metabolism, and not of carbohydrate utilization alone, that the entire diet and maintenance of the entire body mass constitute a load upon the internal function of the pancreas, and that accordingly in the treatment of diabetes increase of diet and of body weight increases the strain upon this function, and reduction of the total diet and weight relieves this strain more effectively and permanently than reduction of carbohydrate alone" Emphasis thus was placed by Allen both on continuous freedom from glycosuria and on keeping the body weight well below the normal weight of the given individual. The advantage of maintaining the urine sugar free had been recognized by many other investigators, but to maintain it so was considered impossible in severe cases without danger from acidosis, the obvious desirability of preserving the body weight had prompted previous authorities to supply food in excess of the patient's tolerance To conduct successfully the Allen treatment, it became necessary to measure food with considerably greater precision than had been done before, tables of food values assumed importance and special food scales were introduced. The thrice cooking of vegetables, with discarding of water, was resorted to in severe cases. The Allen regimen was widely adopted in American clinics between 1914 and 1922. Joslin has referred to this period as the "Allen Era" The better clinical results were evidenced by appreciable prolongation of the lives of patients and a diminished incidence of deaths attributable to diabetic coma

Petrén, in 1920, treated severe diabetes successfully with diets in which fat, principally butter, supplied most of the calories, and intake of both protein and carbohydrate was rigidly restricted His procedure was based primarily on the observation of Naunyn that excess of protein depressed the tolerance. Petrén demonstrated that nitrogen equilibrium was maintained and thus that the protein-sparing effect of fat was comparable to that of carbohydrate, also that formation of ketone as well as glycosuria could be prevented if the calories were adequately supplied by fat

Newburgh and Marsh, in the same year as Petrén, arrived independently at the same conclusions. They advocated diets very low in carbohydrate and protein, with calories provided

advocated by Donkin, who in 1863 gave skimmed asses' milk as an exclusive food, in an amount of 4 to 4 5 liters a day. Cow's milk was preferred by later advocates of this treatment.

The earliest of the carbohydrate "cures" was the "rice cure" in 1868 of von Düring. The "potato cure" of Mossé and the "oatmeal cure" of von Noorden were introduced in 1902. Other similar "cures" followed, eventuating in the "mixed cereal cure" described by Falta, in 1920.

The advocates of these high carbohydrate diets stated that starches of various kinds were better tolerated when boiled than when baked as breads and that starch was better tolerated when given alone or only with fat. A great deal of individualizing was necessary; dieting was a "trial and error" procedure, differing greatly with each patient. The alternating of one diet with another was advised. The von Noorden diets were thus alternated according to the indications presented by the individual patient; for example, six days of a standard, strict diet, with or without a measured amount of white bread or its equivalent, depending on the case, followed by one day of a fat-poor, vegetable diet, or a fast day, another six days of the standard strict diet, then an oatmeal day. Occasionally several oatmeal days were ordered in succession, preceded usually by a day or days of a diet restricted in carbohydrate, and followed by one or two fast days. The alternation of diets was based on the theory that the glycogenic mechanism of the liver was strained in one direction by one diet and in another direction by another; the alternation was supposed to provide the opportunity for successively relieving one strain after another.

Guelpa, in 1913, proceeding from the point of view that diabetes depended on auto-intoxication, resorted to longer fasts. three days of fasting accompanied by purgation, followed by a milk day, then a vegetable day, and then a gradual return to a more liberal diet The process was repeated when necessary. Allen, in 1914, based his similar but more systematic procedure on observations of benefit from fasting after subtotal pancreatectomy of dogs Allen's method involved an initial period of fasting of from one to ten days, or more, until the urine became sugar free, then a gradual addition of vegetables and later of fruits, meat and fat. Fast days were interposed whenever any trace of sugar

was found in the urine. Allen wrote that his experiments were begun "with a view to the possibility that diabetes is a disorder of the total metabolism, and not of carbohydrate utilization alone, that the entire diet and maintenance of the entire body mass constitute a load upon the internal function of the pancreas, and that accordingly in the treatment of diabetes increase of diet and of body weight increases the strain upon this function, and reduction of the total diet and weight relieves this strain more effectively and permanently than reduction of carbohydrate alone." Emphasis thus was placed by Allen both on continuous freedom from glycosuria and on keeping the body weight well below the normal weight of the given individual. The advantage of maintaining the urine sugar free had been recognized by many other investigators, but to maintain it so was considered impossible in severe cases without danger from acidosis; the obvious desirability of preserving the body weight had prompted previous authorities to supply food in excess of the patient's tolerance To conduct successfully the Allen treatment, it became necessary to measure food with considerably greater precision than had been done before, tables of food values assumed importance and special food scales were introduced The thrice cooking of vegetables, with discarding of water, was resorted to in severe cases. The Allen regimen was widely adopted in American clinics between 1914 and 1922. Joslin has referred to this period as the "Allen Era" The better clinical results were evidenced by appreciable prolongation of the lives of patients and a diminished incidence of deaths attributable to diabetic coma.

Petrén, in 1920, treated severe diabetes successfully with diets in which fat, principally butter, supplied most of the calories, and intake of both protein and carbohydrate was rigidly restricted. His procedure was based primarily on the observation of Naunyn that excess of protein depressed the tolerance. Petrén demonstrated that nitrogen equilibrium was maintained and thus that the protein-sparing effect of fat was comparable to that of carbohydrate, also that formation of ketone as well as glycosuria could be prevented if the calories were adequately supplied by fat.

Newburgh and Marsh, in the same year as Petrén, arrived independently at the same conclusions They advocated diets very low in carbohydrate and protein, with calories provided

mainly in fat. The important features of the methods of Petrén and Newburgh and Marsh were that they supplied more nearly adequate calories and that they overcame the earlier fear that the feeding of fat would precipitate dangerous acidosis. Accurate measuring of the portions of food was demanded by the regimen of Newburgh and Marsh, as was also adjustment of total calories to the metabolic requirements of the individual.

The discovery of insulin did away with the necessity of extreme dietary restrictions, and thus overcame the principal shortcoming of all previous diets in which nutrition was sacrificed, perforce, to avoid more serious disaster. While many authorities of today believe that moderate limiting of carbohydrate and protein is still desirable, and others that the intake of fat and total calories should be curtailed, the essential requisites to reasonably effective management can now be met by diets that are palatable and satisfactory, as well as requisite in all nutritional particulars

DIETS OF THE PRESENT

The newer knowledge of nutrition throws into rather painful relief the inadequacies of the older diabetic diets. It is completely unreasonable to suppose that diabetic patients need fewer calories, or less calcium, or less of any of the several vitamins than well men, and yet so heavy on us lies the hand of a past, when diabetic patients had to starve to live, that few physicians have had the temerity to depart entirely from practices involving the principle of undernutrition. Fortunately, few patients ever adhere rigidly to inadequate diets. Natural cravings for essential nutrients are difficult to resist. The blame for broken diets more often is the physician's for planning insufficient diets than the patient's for refusing to follow a diet which provides inadequately for his maintenance.

The requirements for the adequate nutrition of normal men and children, applicable with no less force in diabetes, are given as follows in a publication of the Council on Foods of the American Medical Association.

Requirements for adequate nutrition (Council on Foods, American Medical Association)—The standard daily allowance for a man of average weight (about 154 pounds [69.9 kg.]) and doing a moderate amount of muscular work is as follows: protein, 70 gm., calories, about 3,000 (the 70 gm of pro-

tein will provide 280 calories, the remainder are derived from carbohydrate, 4 calories per gram, and from fat, 9 calories per gram), calcium, 0.7 gm.; phosphorus, 1.3 gm.; iron, 12 mg.; vitamin A, at least 2,000 international units (some authorities suggest much higher amounts), vitamin B_1, at least 300 international units (probably more would be better); vitamin C, about 600 international units (300 units per day will prevent the development of scurvy); and vitamin G, about 600 Sherman-Bourquin units.

The caloric requirements vary with body weight and the amount of muscular work done. The larger the individual, in general, the more calories are needed. An active person engaged in strenuous labor might consume as much as 5,000 calories in a day. Measurements of the food consumed by workers in lumber camps have shown values greater than 8,000 calories in a day. Sedentary individuals require much less; 2,500 or even fewer would meet the needs of many persons doing no manual labor.

Caloric allowances for women average about 20 per cent less than those for men, chiefly because of their smaller size. The requirements for children are less when stated as the total number of calories, but a great deal more when computed in terms of calories per unit of body weight. Thus, a boy ten years of age will require approximately 2,100 to 2,700 calories. At the age of sixteen he will require from 2,700 to 4,000, usually more than his father, unless the latter is doing heavy manual labor.

Unlike total caloric requirements the protein, mineral and vitamin needs are not greatly changed by differences in activity. Requirements change with age and size, but these tend to offset one another so that the standard mineral allowances for children are 1 gm. of calcium, 1 to 1.5 gm. of phosphorus and about 5 to 10 mg. of iron. The customary protein allowance is approximately 1 to 2 gm. of protein per pound of body weight. Children have to grow, and over and above their maintenance requirements they need liberal allowances of protein, minerals and vitamins for the production of new body substances of all kinds. Aside from general physical fitness, one of the signs of good nutrition is normal growth during childhood and maintenance of normal weight in adult life.

The admonition of the Council closes with the suggestion that the diet of an adult should contain at least 1 pint (500 c.c.) of milk, two servings of vegetables, two servings of fruit, one or two servings of protein foods, and a serving of whole grain cereal. It is possible to deviate from this prescription, for instance to do without milk, but when any of the "protective foods" are omitted, other foods must be chosen as substitutes in amounts sufficient to replace what otherwise would be lost—in the case of milk, calcium, protein and vitamin A. Without using whole wheat flour in place of white flour it is difficult to construct a diet which is more than borderline in its content of vitamin B_1.

When diabetic diets are planned with these general principles firmly in mind, children grow and develop satisfactorily, patients are protected from infections, degenerative disturbances are post

poned, and normal bodily and mental vigor are promoted. But how many physicians adhere to these principles? A few years ago I secured, from four large diabetic clinics, diet prescriptions for a hypothetical male patient, a white-collar worker forty years of age, 5 feet, 5 inches (165 cm.) in height and of standard weight. The calories ranged from 1,780 to 2,280. Obviously if the clinic prescribing the largest number of calories was right, the other prescriptions were deficient.[1] Deficiency in calories is not the only shortcoming of low calorie diets. Unless unusual precautions are taken in planning menus, other nutritional factors will be low, so that a low level of calories generally means semi starvation in such items as calcium and one or more of the vitamins.

My experience teaches that normal nutrition cannot possibly be maintained in a moderately active individual with fewer calories than are represented by the sum of those demanded to provide for the basal metabolism ("basal" calories) plus a quota for activity equal to one-half of the basal calories. The conclusion depends partly on many thousands of observations of intelligent diabetic patients who were fully instructed, weighed their foods and adhered faithfully to their diets. Partly it is based on calculations of the number of calories derivable from the fat lost during periods of supervised weight reduction in cases of obesity. The standard dietary procedure in the Section of Metabolic Therapy of The Mayo Clinic was planned from this experience. In what follows in this chapter it will first be described. Other types of diet planning will be considered later.

STANDARD DIABETIC DIETS, SECTION OF METABOLIC THERAPY, THE MAYO CLINIC

Among adult patients with diabetes of proved mildness satisfactory control can be obtained merely by avoidance of sweetened foods, together with enough restriction of starch and fat to pre-

[1] Joslin wrote that few adult patients need more than 30 calories per kilogram of weight in twenty four hours (2100 calories for 154 pounds), but that such an allowance is inadequate in most cases is suggested by his subsequent statement, namely: "In computing the calories which are to be given a patient when he goes home, one should always have this point in mind that the chances are overwhelming that the diet will be enriched, often innocently with fat, rather than decreased, and consequently the calories of a given diet in the hospital, as a rule, are distinctly less than the actual calories which such a diet in the home represents"

vent overweight. When such measures alone prevent glycosuria, there is no need for insulin. When they fail, it is wise to avoid the risk of malnutrition, which more rigid restriction might entail, and instead to turn to insulin. In cases of severe diabetes, and almost always with diabetes of children, insulin is indispensable.

The diet plan which we have adopted effects systematic individualization in the provision of calories for maintenance The estimate of total energy requirement is based not only on "ideal" weight,[2] but also on height, sex, age and type of occupation. The calculation is simplified by a nomogram,[3] with which the normal basal metabolism for twenty-four hours for the appropriate age, sex, height and weight is readily determined A definite percentage increment is made for the extra calories required for muscular activity: For "room rest" 10 to 20 per cent is added, for very light work, 20 to 30 per cent; for housekeepers, operators of machinery and white-collar occupations, 50 per cent, for manual laborers and soldiers, 60 to 70 per cent, and for children, 60 to 100 per cent Subsequent gain or loss of weight will tell whether the extra calories allowed for work have been estimated correctly. It never is wise to permit the weight to rise above the ideal If this occurs, the diet should be readjusted by omitting from it some of the butter or butter equivalents. If the patient loses weight or fails to gain, when gaining is desirable, the butter equivalents should be increased. The complaint of hunger should not lead the physician to prescribe an increased allowance of food until he assures himself that the hunger is not the result of excessive doses of insulin. Less insulin may be the proper remedy rather than more food.

The next step is the selection of amounts of food which will

[2] The "ideal" weight is derived from the standard weight as given in the "Height, weight and age tables" of the Medico-Actuarial Mortality Investigators (see Appendix). If a patient is small chested and small boned, the ideal is assumed to be 10 per cent less than the standard weight as read from the table If he is heavily built, with broad shoulders and big bones and muscle, it is assumed to be 10 per cent more The ideal rather than the actual weight of the patient is used in calculating his caloric requirement because then if he is underweight more calories will be supplied by the diet than are required for his maintenance and gradually he will gain to the ideal, whereas if he is overweight he gradually will reduce

[3] A copy of this nomogram is inserted in the Appendix Additional copies may be procured from The Whiting Press, Inc., 211 West Center Street, Rochester, Minnesota.

provide the calories demanded and adequately supply proteins, vitamins and salts. This step is simplified by a series of skeleton diets (see Appendix). The selection of the appropriate one is made according to the calories demanded. The amount of butter or butter equivalent which appears after the number of calories, when added to the foods in the skeleton, completes the diet. The skeleton diets differ for men, women and children to meet the different food habits of the sexes and to provide the special requirements of childhood. They are all constituted, however, of specified amounts of vegetables, fruit, cereal, bread, cream, milk, eggs and meat. The use of graham (whole wheat) bread is advocated because of its content of the vitamin B complex.

The third step is the planning of menus. The three principal meals usually are made to contain equal proportions of the total amount of carbohydrate, protein and fat for the day, but some freedom is permitted and in some cases, particularly when protamine-zinc insulin is used, better control of glycosuria may be obtainable by dividing the quota for the day into four or five meals Finally, to prevent monotony, appropriate substitutions are permitted for the items of food named in the diet. For this purpose an extensive list of equivalents is supplied, including a considerable number of recipes (see Chapter VIII).

The use of special foods[4] is discouraged, with one exception. So-called water-packed or juice-packed fruits are used in preference to the ordinary canned products, because the latter contain a widely variable amount of added sugar—from 20 to 50 per cent Dried fruits are omitted for the same reason.

[4] A large number of special foods designed for use in diets restricted in dextrose formers are on the market The availability of insulin makes them no longer necessary for the treatment of diabetes and, with the exception of water-packed and juice-packed fruits, none is recommended Usually they are expensive; many of them, furthermore, although low in carbohydrate, contain relatively large amounts of protein and thus provide in metabolism an amount of dextrose which is but little less than that contained in ordinary bread Among special products accepted by the Council on Foods of the American Medical Association are canned, water packed vegetables, canned [illegible] fruit juice, gelatin dessert powd [illegible] fast cereal and flour and [illegible] India gum and mineral oil [illegible] and carriers of butter and [illegible] special purpose foods must state the approximate protein, fat and carbohydrate content for acceptance by the Council Detailed information about them can be obtained from the Council office and information regarding the composition of many other commercial diabetic foods is given in Bulletins 220 and 236 of the Connecticut Agricultural Experiment Station, New Haven, Connecticut.

Condiments.—Pepper and other spices are without significant food value. The same is true of vinegar and extract of vanilla.

Sweetening agents.—Saccharin is permitted for sweetening purposes, but too much saccharin, or saccharin added to acid foods while they are cooking, imparts a bitter taste. It should be used, therefore, in correct amounts and added to cooked foods after the food has been removed from the fire. Glycerin used for sweetening is neither satisfactory nor better utilized than sugar. Honey, contrary to old beliefs, is utilized by diabetics no better than cane sugar.

Beverages.—Coffee and tea are permitted in moderate amounts, such as one cup of coffee or one cup of tea at a meal. Clear tea and coffee have little or no food value and therefore are not counted in calculating the composition of the diet. Other beverages are permitted only if their content of sugar is known and counted in the calculation of the diet.

Alcoholic beverages.—Sour wines add greatly to the attractiveness and palatability of the diet. Their content of carbohydrate is insignificant and the alcohol they contain adds to the fuel value of the diet in much the same way as fat. Used in moderation they are highly desirable. Sweet wines and beers are less suitable because the quantity of carbohydrate they contain is variable. Unsweetened distilled liquors, such as brandy and whisky, injurious if taken immoderately, are serviceable when used judiciously as appetizers and tonics. Sweetened cordials and liquors are not permitted.

Tobacco.—The abuse of tobacco is undoubtedly harmful. Considerable moderation is advisable, therefore, in indulgence in tobacco by diabetic patients. In cases of diabetes with associated occlusive vascular disease the use of tobacco in any form is prohibited.

Weighing foods.—The patient is directed to weigh all the foods he eats (gram scale) until he has acquired sufficient experience to estimate accurately the weights of the portions called for by his diet order. It takes at least three months to learn to eat quantitatively, without food scales, and even after this time patients ought to resume the weighings on one day of each week to correct erroneous estimations.

Use of food nomogram; (example).—A male clerk of average body build is thirty years old, 68 inches (172.7 cm) in height, and without shoes or coat

weighs 120 pounds (54 5 kg). The standard weight for a man of this age and height is looked for in the "Height, weight, age tables" of the Medico-Actuarial Investigation (see Appendix). It is 152 pounds (69 1 kg).[1] The patient weighs only 120 pounds, but he is of average body build; therefore the standard weight for him is considered ideal and with a diet planned to meet the requirements of 152 pounds he ought gradually to gain to this ideal.

Turning to the food nomogram[2] the point representing 152 pounds (69 1 kg.) is located on scale I and the point representing 5 feet 8 inches (68 inches) on scale II. The two points are connected with a straightedge (ruler) and the point where this edge crosses scale III is noted. It is at 1 8 This value, which is not of immediate concern, represents the surface area of the individual in square meters. Next the point on scale IV which corresponds to the patient's age and sex is located and connected by means of the straightedge with the point previously found on scale III. The edge now crosses scale V at a point representing 1,750 calories This is the number of calories necessary to maintain the basal metabolism of this patient for twenty-four hours It also represents the food energy required by him at rest in bed

The patient is a white-collar worker, therefore to provide the extra calories needed for muscular activity these "basal" calories are augmented by 50 per cent (see p 115) The point, + 50, is spotted on scale VI of the food nomogram and the straightedge is placed to join the point previously found on scale V, whereby the total calories of the food to be allowed can be read on scale VII In this example they are 2,625

Next comes the selection of the standard diet (see Appendix) The calories decided on were 2,625; therefore diet IV for men, under which this number appears, is chosen. It provides vegetables (of the group containing 3 per cent of carbohydrate), 400 gm; fruit (of the group containing 10 per cent carbohydrate), 300 gm; vegetables or fruits (of the groups of these containing 20 per cent carbohydrate), 100 gm; cereal, 20 gm; bread, 120 gm.; cream (with 20 per cent butterfat), 300 gm; milk, 200 gm; bacon, 15 gm; eggs, 2, meat, 125 gm, and butter or equivalent, 80 gm. The calories of the completed diet number 2,606 The grams of carbohydrate are 167, those of protein 84 and those of fat 178

From these foods the menus of three or more meals are planned as follows:

STANDARD DIET 2,600 CALORIES

	Breakfast	
	Gm.	Approximate measure
Fruit, 10 per cent, orange juice	100	½ glass
Cereal, oatmeal, dry	20	1 serving
Bread	40	2 small slices
Butter	15	1½ squares
Bacon	15	3 strips
Egg		2
Cream (20 per cent butterfat)	100	½ cup

Dinner		
Vegetable, 3 per cent, cabbage and green pepper salad	50	½ cup
Vegetable, 3 per cent, tomato	150	¾ cup
Fruit, 10 per cent, peaches	100	½ cup
Bread	40	2 small slices
Vegetable, 20 per cent, potato	100	1 small
Butter	20	2 squares
Mayonnaise	15	1 tablespoon
Cream (20 per cent butterfat)	100	½ cup
Milk	100	½ cup
Meat, roast beef	75	1 large serving
Supper		
Vegetable, 3 per cent, lettuce.	50	¼ small head
Vegetable, 3 per cent, asparagus	150	1 large serving
Fruit, 10 per cent, strawberries	100	½ cup
Bread	40	2 small slices
Butter	15	1½ squares
Mayonnaise	15	1 tablespoon
Cream (20 per cent butterfat)	100	½ cup
Milk	100	½ cup
Meat, cold chicken	50	1 serving

Finally, substitutions are arranged for each of the various items of this standard diet in order to avoid monotony (see Chapter VIII)

REDUCTION DIETS

When a patient is grossly overweight, very great advantage may attend an expeditious reduction of his body weight. Thereafter, not infrequently the tolerance will have improved so much that control will be possible merely by omitting sweets and sweetened foods—provided always that the body weight is not permitted to increase again. In these cases we have used with advantage the procedure of Evans and Strang All food must be weighed Satisfactory reduction of obesity rarely can be accomplished otherwise. The diet is constructed of lean meats, greens and citrus fruits to provide only 580 calories and deficiency of vitamins and calcium is avoided by prescribing dried brewers' yeast, thiamin, a vitamin A concentrate and calcium phosphate [5]

This diet has been followed for months by obese patients, with a total loss of body weight of more than 100 pounds (45.4 kg), and when the supplementation prescribed has not been neglected

[5] A customary prescription calls for the daily addition of 12 tablets of a brewers' yeast accepted by the Council on Foods of the American Medical Association, 1 mg

no ill effects have been observed. A sample menu is appended Substitutions for the various food items of the diet are permitted from the list of equivalents provided for the standard diabetic diets (see Chapter VIII). No substitute is permitted for the skimmed milk.

Sample Menu for Reduction Diet; 585 Calories

Breakfast	Gm
Fruit, 10 per cent, orange, sliced	100
Bread, whole wheat	10
One egg, soft boiled	
Dinner	
Vegetable, 3 per cent, string beans	75
Vegetable, 3 per cent, lettuce, tomato and cucumber salad	75
Fruit, 5 per cent, peaches	100
Meat, broiled steak, lean, no visible fat	90
Supper	
Vegetable, 3 per cent, asparagus	75
Vegetable, 3 per cent, celery hearts, radishes	75
Fruit, 5 per cent	100
Milk, skimmed	200
Meat, lamb chops, lean, no visible fat	90

DIETS FOR PATIENTS WITH HYPERLIPEMIA

Abnormal elevation of the values for blood lipoids, notwithstanding many statements to the contrary, is not a characteristic accompaniment of diabetes. The subject will receive ample consideration later. A disturbance of fat metabolism exists, however, in some cases of diabetes, as well as independently in patients with no diabetes, and in this disturbance high values for blood lipoids are found. They are associated usually with evidence of atheromatosis and frequently, but not always, with xanthomatosis For such cases a special diet is indicated which is rigidly restricted in animal fat (see p. 337). Two diets illustrative of what we prescribe for these patients follow. The various items contained are susceptible of substitution according to the procedure recommended for the standard diet, but in making substitutions, attention must be given to securing foods that contain no cholesterol, lecithin, or other animal lipoid. The calories are adjusted to the requirement of the individual by adding or subtracting from the allowances of vegetable oil. Such diets must be supplemented with a preparation of vitamin A.

Two Diets for Hyperlipemia

	Diet 1, gm	Diet 2, gm
Vegetables, 5 per cent	400	400
Fruit, 10 per cent	200	200
Vegetables or fruits, 20 per cent	100	200
Cereal (dry)	14	20
Bread	100	200
Milk, skimmed	600	600
Egg	2 whites	2 whites
Meat, lean*	50	100
Jelly	30	40
Sugar	45	45
Composition		
Carbohydrates	215	301
Fat	17	26
Protein	55	79
Calories†	1213	1754

* There should be no visible fat in the meat or fish used

† For extra calories to meet the requirement of the individual, vegetable fat is added as vegetable oil or products made only from vegetable oils, such as vegetable lards and vegetable margarines All provide approximately 8 calories per gram These diets must be supplemented with a preparation of vitamin A carrying a minimum of fish oil

DIETS FOR CHILDREN

It is of extraordinary importance to emphasize to parents that the diets of children need readjustment not less frequently than once each year. In several cases dwarfism has been due to failure to increase these diets in proportion to the increasing demands of advancing age.

The food calories required for children are calculated with the food nomogram from the ideal weight, and the height, age and sex, as was described before for cases of adults. One exception is made. When the height of the child is less than the average height for the given age and sex in the Baldwin-Wood tables (see Appendix) the average rather than the actual height is adopted For example: The range of heights for a boy eight years of age is given in this table as from 42 to 56 inches The mean height, thus, is 49 inches and, if the patient is a boy eight years of age and measures less than this, 49 inches and not his actual height is used in the calculation. The weight used in the calculation (nomogram) is that which is given in the Baldwin-Wood tables for the mean height. In the case of boys eight years old it is 55 pounds.

The protein in the diet for undersized children is made 20 per cent greater than that shown in the standard diets. The additional protein is given in the form of extra meat; the calories of the addition are balanced by omitting an isocaloric amount of fat.

Diets for children who are not under average height are planned on the basis of actual heights and ideal weights for their heights.

OTHER TYPES OF DIET PLANNING

The amount of carbohydrate in the standard diets of the Section on Metabolic Therapy of The Mayo Clinic varies from 121 to 167 gm., that of protein from 57 to 84; the fat—since fat is relied on to supply most of the calories—may amount to more than 200 gm. in some cases. In carbohydrate, therefore, these diets are neither very low nor very high; their content of fat is relatively high.

The wisdom of including much fat in diabetic diets has been challenged, and in a number of clinics diets restricted in fat are preferred. Joslin, whose diets are not appreciably richer in carbohydrate than ours, holds the fat in them down by continued adherence to the principle of undernutrition. Others have turned to regimens providing much more carbohydrate. A few, like Rabinowitch, have advocated diets containing even less fat than is included in the foods consumed by nondiabetic individuals.

The introduction of insulin in 1923 opened the way for continuous feeding of diets rich in carbohydrate; Sansum and his associates, independently, Geyelin (1926), Porges and Adlersberg and later Rabinowitch and others proceeded to take the fullest advantage of the opportunity. In some instances more starch and sugar have been recommended than are contained in a normal diet, and the claim has been made that the well-being of patients was improved, that the incidence of tuberculosis and the danger of acidosis were diminished, and that the progress of arteriosclerosis was impeded. The diets advocated by Porges and Adlersberg were rich in carbohydrate and in protein. Addition of fat was said to affect the metabolism unfavorably even if the number of calories was not increased.

The evidence that the welfare of patients is improved by increasing diets in carbohydrate and protein and restricting fat is not impressive. Our reasons in The Mayo Clinic for not adopting

such diets are as follows: (1) Most patients are well satisfied with our standard diets and have been less well satisfied when the allowance of fat has been restricted, as demanded by the advocates of high carbohydrate diets Diets rigidly restricted in fat not only are unpalatable; they also are inadequate or borderline nutritionally. (2) Growth and development of the children who have followed our instruction have been satisfactory and the resistance of both children and adults to infections and trauma[6] has not suggested that our diets have been inadequate nutritionally. (3) For reasons to be given later we have not been convinced that higher fat feeding seriously decreases the life expectancy of patients who are adequately supplied with insulin, or promotes the development of arteriosclerosis. (4) Use of high carbohydrate diets did not simplify dietetic procedure; indeed, it seemed to us to complicate management by necessitating more precision in the measuring of amounts of food than otherwise was necessary.

Free diets—Other authors, particularly in Europe, have reported impressively satisfactory results from "normal" or what are designed as "free" diets, in which diet therapy is replaced almost wholly by the substitution therapy of insulin. In the follow-up records of 900 patients under treatment during a period of ten years Geyelin (1935), who prescribed diets essentially "free," reported no serious difficulties with acidosis, no development of tuberculosis and a low incidence of cardiovascular disease The pediatrists in Europe generally have adopted the free diet which Stolte was first to recommend and, among those who have reported are Söderling, Ercklentz, Muller and Lichtenstein. The last named wrote in an American journal. He had treated fifty children; the diabetes of all of them was considered grave, inasmuch as in all of them coma or threat of coma had occurred once or repeatedly. The free diet had been used for a time, varying from one-half to five years. Results had been excellent, intercurrent infections were overcome more easily and exerted much less influence on the metabolism than formerly when diets were restricted. As a consequence, children who previously were

[6] The low mortality rates for diabetic patients subjected to operations in The Mayo Clinic before 1932 have not been matched elsewhere, or since then in The Mayo Clinic. For the period from October, 1921 to October, 1932 inclusive, in which diabetic diets contained less carbohydrate and more fat than later, 1028 major and 1058 minor surgical procedures were performed with a total of sixty nine deaths, a mortality rate of 3.3 per cent (Walters and associates)

chronically returning guests at the hospital, often several times every year, could be cared for almost without exception outside the hospital.

Is there, in fact, anything in the diabetic state to contraindicate a normal diet? I can think of three valid objections, but the first of these, as Boyd has pointed out, is economic and not physiologic. It is claimed by the advocates of high carbohydrate and free diets that increasing the intake of carbohydrate frequently does not necessitate larger doses of insulin. This, in my experience, is true in only a small proportion of cases; nevertheless, insulin now is so much less costly than it was that the disadvantage of having to use more of it is disappearing. I agree with Boyd that while economic conditions may necessitate a compromise, such compromises should be the exception, not the rule, and that the aim in nutrition should be, not indispensable minimums but optimal standards.

My second objection to free diets also is a minor one. Geyelin (1935) has pointed out that a normal diet is one in which the proportions of carbohydrate, protein and fat are approximately 4:1:1 respectively, and it has been my experience, although not his, that excretion of sugar after meals becomes excessive when as much carbohydrate as this is taken. Wider fluctuation of blood sugar levels results, and of the harmlessness of wide fluctuations *I am not convinced.*

My third objection is important. Free diets and diets in which the proportions of carbohydrate, protein and fat are *4:1:1*—eminent authorities agree that these proportions of the major food factors are found in the average diets of so-called normal adults and children in this country and Europe—containing, as they do, large amounts of starches and sugar, are frequently deficient or borderline in their content of protective foods A completely free selection of foods, under the unnatural conditions of modern society, *is likely not to result in an optimal* diet for anyone,[7] and

[7] "Nutritional knowledge has evolved from a random hodge podge to something almost intelligible Reasons have been found for the *deleterious effects of* civilization's purifications Lack of knowledge can no longer be an excuse for a high incidence of malnutrition, or for the many diseases resulting from dietary deficiencies Yet few medical schools give or require a course in nutrition Some sketchy information is picked up incidentally by the medical student, but a comprehensive grasp of the subject is not insured" The quotations are from C. C. and S M *Furnas*

there are good reasons for believing that the requirement for certain of the vitamins actually is increased by diabetes. Thus, a food mixture on which nondiabetic persons might "get by" may be inadequate nutritionally for diabetic persons.

Therefore, although I am prepared to admit the desirability of greater liberality in the dietotherapy of diabetes, as compared with the practice of several years ago, I still insist on dietary guidance in all cases. The favorable nutritional results we have obtained with our standard diets may be attributable to the large amounts of protective foods which they have contained and, if we turn to freer diets, we must continue to provide training of patients to promote optimal as opposed to passable nutrition. We have found that patients who have received full instruction in our standard diabetic diet later can be allowed a free selection of food with considerable success, but that untrained patients do badly on such free diets. The trained patient acquires satisfactory food habits by following a planned diet for a year or two, and these permit him to make wise selections of food when restrictions later are withdrawn. The untrained, undisciplined patient on an unrestricted diet soon gets into trouble

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My second objection to free diets also is a minor one. Geyelin (1935) has pointed out that a normal diet is one in which the proportions of carbohydrate, protein and fat are approximately 4:1:1 respectively, and it has been my experience, although not his, that excretion of sugar after meals becomes excessive when as much carbohydrate as this is taken. Wider fluctuation of blood sugar levels results, and of the harmlessness of wide fluctuations I am not convinced.

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CHAPTER VIII

DIABETIC COOKERY: SUBSTITUTIONS FOR FOODS IN THE STANDARD DIET

In the preparation of meals for the patient in the home, time can be saved by weighing the day's allowance of butter, milk, cream, eggs, bread and fresh fruit before the first meal Weighed portions of cooked vegetables, cooked cereals and meats can then be removed from the supply prepared for the family before any trimmings have been added, and these portions can be prepared for the patient as desired, with the butter, milk, cream, and so forth, previously set aside. Graham (100 per cent whole wheat) bread is recommended because of its content of vitamin B complex.

The standard diabetic diets, described in Chapter VII and shown in the Appendix, are constructed of given amounts of a limited number of foods: vegetable, fruit, bread, cream, milk, eggs, meat and butter. Monotony is avoided by making suitable substitutions for any or all of these items according to the following directions, and by making use of the recipes provided herewith.[1]

SUBSTITUTIONS FOR VEGETABLES AND FRUITS

In place of 100 gm. (½ cup) of 3 per cent vegetable one of th following may be used:

	Gm	Approximate measu
1 Vegetable, 6 per cent[2]	50	⅓ cup
2 Fruit, 5 per cent	60	¼ cup
3 Fruit, 10 per cent	30	⅛ cup
4 Vegetable or fruit, 15 per cent	20	⅛ cup scant
5 Vegetable or fruit, 20 per cent	15	
6 Any one of these salads		

[1] These directions and recipes are reproduced from the sixth edition "Primer for diabetic patients" For most of this material I am indebted t A Foley

[2] Per cent here refers to content of carbohydrate For classification tables according to their percentage content of carbohydrate see table 10, A on p. 408

Perfection Salad	Gm.	Approximate measure
Lettuce	20	2 or 3 leaves
Tomato juice	50	¼ cup
Celery, cubed	15	⅛ cup
Cabbage, chopped	15	¼ cup
Vinegar		½ teaspoon
Gelatin		½ teaspoon
Stuffed olives		3 slices

Salt and pepper to taste.

Soak the gelatin in one tablespoon of cold water Add the boiling tomato juice and allow to cool When it begins to thicken add the vegetables and chill

Fruit Salad.	Gm.	Approximate measure
Lettuce	20	2 or 3 leaves
Fruit, 5 per cent (any kind)	50	¼ cup

Pickled Beet Salad.	Gm	Approximate measure
Lettuce	20	2 or 3 leaves
Pickled beets	40	¼ cup (scant)

Note Sugar must not be used in pickling beets.

Raw Carrot Salad	Gm.	Approximate measure
Lettuce	20	2 or 3 leaves
Celery, cubed	20	⅛ cup
Raw carrot, grated	30	⅛ cup

Pineapple and Carrot Salad	Gm.	Approximate measure
Lettuce	20	2 or 3 leaves
Pineapple, shredded	15	
Carrot, grated	20	⅛ cup (scant)
Gelatin		⅓ teaspoon
Water, cold		2 tablespoons
Water, boiling		⅛ cup

Shredded Lettuce and Orange Salad	Gm.	Approximate measure
Lettuce	20	2 or 3 leaves
Orange, cubed	25	⅛ cup

In place of 100 gm. (½ cup) of 6 per cent vegetable, one of the following may be used.

	Gm.	Approximate measure
1. Vegetable, 3 per cent	200	1 cup
2. Fruit, 5 per cent	120	½ cup
3 Fruit, 10 per cent	60	¼ cup
4. Vegetable or fruit, 15 per cent	40	¼ cup (scant)
5 Vegetable or fruit, 20 per cent	30	⅛ cup

In place of 100 gm. (½ cup) of 5 per cent fruit, one of the following may be used·

	Gm.	Approximate measure
1. Vegetable, 3 per cent	165	⅞ cup
2 Vegetable, 6 per cent.	85	⅓ cup
3 Fruit, 10 per cent	50	¼ cup
4 Vegetable or fruit, 15 per cent	35	⅙ cup
5 Vegetable or fruit, 20 per cent	25	⅛ cup
6 Soda crackers	7	1
7 Bread	10	½ small slice

In place of 100 gm. (½ cup) of 10 per cent fruit one of the following may be used:

	Gm	Approximate measure
1. Vegetable, 3 per cent	350	1¾ cup
2 Vegetable, 6 per cent	165	⅞ cup
3 Fruit, 5 per cent	200	1 cup
4 Vegetable or fruit, 15 per cent	65	⅓ cup
5 Vegetable or fruit, 20 per cent	50	¼ cup
6 Cereal, dry	12	1 very small serving
7 Soda crackers	14	2
8 Bread	20	1 small slice

In place of 100 gm. either of 20 per cent fruit or 20 per cent vegetable one of the following may be used.

	Gm	Approximate measure
1 Fruit, 10 per cent	200	1 cup
2 Vegetable or fruit, 15 per cent	135	⅔ cup
3 Soda crackers	28	4
4 Flour	26	
5 Bread	40	2 small slices
6 Cereal, dry	25	1 serving

Cooked fruits.—When a serving of fruit is to be cooked or baked, weigh it raw, add water and cook. The juice as well as the fruit should be served.

Dried fruits.—Dried fruits contain large and inconstant amounts of sugar and therefore should be avoided.

SUBSTITUTIONS FOR BREAD

In place of 20 gm. (1 small slice) of bread one of the following may be used:

	Gm	Approximate measure
1. Vegetable, 3 per cent	350	1¾ cup
2 Vegetable, 6 per cent	176	⅞ cup
3 Fruit, 5 per cent	212	1 cup+
4 Fruit, 10 per cent	106	½ cup
5 Vegetable or fruit, 15 per cent	70	⅓ cup
6 Vegetable or fruit, 20 per cent	53	¼ cup
7 Cereal, dry	13	
8 Soda crackers	14	2
9 Flour	14	3 tablespoons

As all dry cereals have approximately the same composition, you may use cornflakes, puffed rice, shredded wheat, cream of wheat and oatmeal according to your taste. Oatmeal is recommended because of its content of the vitamin B complex. A cooked cereal takes up a large amount of water. If cereal is to be

taken from that cooked for the whole family, prepare it according to the following directions and weigh out seven times the dry weight. Add 120 gm. of dry cereal to 1 quart of boiling water. Bring to the boiling point and cook in top part of double boiler for the required length of time. Now 140 gm. of cooked cereal equals 20 gm. of dry cereal.

SUBSTITUTIONS FOR CREAM

In place of 100 gm. (½ glass) of 20 per cent cream[3] one of the following combinations may be used:

		Gm.	Approximate measure
1.	Milk	100	½ glass
	Butter	20	2 squares
2.	Fruit, 5 per cent.	100	½ cup
	Meat	10	
	Butter	20	2 squares

In place of 230 gm. (½ pint) of 20 per cent cream[3] one of the following combinations may be used:

		Gm.	Approximate measure
1	Egg		1
	Bread	20	1 small thin slice
	Butter	45	4½ squares
2	Egg		1
	Orange	120	1 medium-sized
	Butter	45	4½ squares
3	Milk	230	½ pint
	Butter	45	4½ squares
4	Cream, 40 per cent	100	½ cup
	Egg		1
	Orange	100	1 medium-sized

If the butterfat content of the cream which is bought is 30 per cent and this is to be used in place of 20 per cent cream, the following directions apply:

1. In place of 230 gm. (½ pint) of 20 per cent cream, 230 gm. of 30 per cent cream (½ pint) may be used if 100 gm. of 3 per cent vegetable is added to the diet and 25 gm. of butter omitted

2 In place of 230 gm. (½ pint) of 20 per cent cream, 150 gm. of 30 per cent cream may be used if 100 gm. of milk is added to the diet.

In place of 230 gm (½ pint) of 40 per cent cream (whipping cream) one of the following combinations may be used·

[3] Per cent here refers to content of butterfat

		Gm	Approximate measure
1.	Milk	150	¾ glass
	Butter	100	10 squares
2.	Cream, 20 per cent	150	¾ glass
	Butter	70	7 squares
3.	Egg		1
	Orange	70	¾ medium sized
	Butter	100	10 squares

If the cream which is bought contains 30 per cent butterfat, 230 gm. (½ pint) of it may be used in place of 230 gm of 40 per cent cream, if 25 gm. of butter or equivalent is added to the diet and 100 gm. of 3 per cent vegetable or equivalent is omitted.

In place of 100 gm. of 40 per cent cream 45 gm. of butter or equivalent may be used if 100 gm of 3 per cent vegetable or equivalent is added.

SUBSTITUTIONS FOR MILK

Milk is so valuable a food that substitution of that amount of it called for in the Standard Diet rarely is desirable.

In place of 200 gm. of milk (1 glass) one of the following combinations may be used:

		Gm	Approximate measure
1.	Orange	100	1 medium sized
	Egg		1
2.	Bread	20	1 small slice
	Egg		1
3.	Cereal, dry	15	1 small serving
	Egg		1
4.	Soda crackers	14	2
	Egg		1
5.	Potato	50	½ medium-sized
	Egg		1

Bacon

Bacon may be weighed either raw or cooked. If weighed raw the fat which separates on cooking must be used or substituted for by an equal amount of butter; if weighed cooked the fat which separates on cooking is to be discarded.

In place of 25 gm. of cooked bacon (3 or 4 strips) you may use one egg and 10 gm. (1 square) of butter.

Eggs

Eggs need not be weighed. An average-sized egg contains approximately 6 gm. of protein and 6 gm. of fat.

In place of one egg 25 gm. of meat or equivalent may be used

SUBSTITUTIONS FOR MEAT

Meat should be weighed after it is cooked and in the following pages references to meat will be to cooked meat unless otherwise specified.

Lean meats such as beef, mutton, lamb, veal or fowl are called for in the Standard Diet. If fat meat such at fat beef or pork is used:

—deduct 15 gm. of butter for 75 to 100 gm. of meat.

—deduct 10 gm. of butter for 50 to 75 gm. of meat.

—deduct 5 gm. of butter for less than 50 gm. of meat.

In place of 50 gm. of lean meat, such as beef, mutton, lamb or veal, one of the following may be used:

		Gm.	Approximate measure
1.	Eggs		2
2.	Beef's tongue	60	1 serving
3	Corned beef	70	1 large serving
4	Ham	60	1 serving
5	Liver	50	1 serving
	and bacon	10	1 strip
6.	Dried beef	40	1 serving
	and butter	10	1 square
7	Sweetbreads	60	1 serving
8.	Cheese, American	40	2 cubic inches
9	Sardines (in oil)	50	1 serving

Salmon, tuna fish and mackerel have the same fuel value as meat, but other fish contain less protein and fat and therefore are lower in fuel value. If fish such as halibut, white fish, lake trout and perch, or crab and lobster are to be used:

—take 35 gm of fish and 5 gm. of butter in place of 25 gm. of meat.

—take 70 gm. of fish and 10 gm. of butter in place of 50 gm. of meat.

—take 105 gm. of fish and 15 gm. of butter in place of 75 gm of meat.

SUBSTITUTIONS FOR BUTTER

The quantity of butter prescribed is probably greater than the patient has been accustomed to. What is not eaten with the

bread may be added to the vegetables or to a broth. Time may be saved in weighing meals if the entire daily allowance of butter is weighed before breakfast. The butter is then used as needed for each meal. A square of butter as usually served in restaurants weighs approximately 10 gm Oleomargarine, butterine, nut margarine, bacon fat, and salad oil contain about the same amount of fat as butter and may be substituted for it. Mayonnaise, French and other salad dressings on the market usually contain variable amounts of sugar or other carbohydrate and therefore are unsuitable for the diet. Mayonnaise, French and cooked salad dressing, when prepared according to the following recipes, may be substituted for butter.

Mayonnaise.	Gm	Approximate measure
Salad oil	400	2 cups
Vinegar		3 tablespoons
Egg yolks		3
Paprika (if desired)		⅛ teaspoon
Salt		¼ teaspoon

Have eggs and oil cold. Beat eggs until foamy, add seasonings Then add a small amount of oil and beat well, then a small amount of vinegar. Continue adding oil and vinegar alternately until mixture begins to thicken. Then add in large quantities, beating constantly. Dry or French mustard and cayenne may be added.

French Dressing:	Gm.	Approximate measure
Salad oil	200	1 cup
Vinegar	100	½ cup
Salt		¼ teaspoon
Paprika (if desired)		¼ teaspoon

French dressing and mayonnaise have the same food value.

Cooked Salad Dressing.	Gm	Approximate measure
Egg yolks		4
Butter	45	4½ squares
Vinegar		5 tablespoons
Water		5 tablespoons
Mustard		1 teaspoon

Salt and pepper to taste

One level tablespoon of cooked salad dressing is equal to 5 gm. of butter (½ square).

Other Substitutions for Butter:

1. In place of 30 gm. of butter 130 gm. of 20 per cent cream may be used if 10 gm. of bread is omitted from the diet.

2. In place of 50 gm. of butter 100 gm. of 40 per cent cream may be used if 100 gm. of 3 per cent vegetable or equivalent is omitted from the diet.

OTHER SUBSTITUTIONS: RECIPES

Broth and Soup

Broth made from beef, veal, mutton or chicken may be used in reasonable amounts at meal time or when a hot drink is desired between meals Bouillon cubes may be used without deducting from other food allowed. A part of the vegetable allowance, cream and butter may be included in a soup.

1. *Noodle Soup:*

	Gm.	Approximate measure
Broth, clear		1 cup
Egg		1
Butter	10	1 square

Beat the egg until stiff and bake in 10 gm. of butter as an omelet; let cool, cut into strips as noodles. Heat the broth and add the noodles. Season with salt and pepper.

When this recipe is used, omit from the meal:

	Gm	Approximate measure
Egg		1
Butter	10	1 square

2. *Tomato Soup:*

	Gm.	Approximate measure
Broth, clear		1 cup
Tomatoes, cooked	80	½ cup (scant)
Onions, uncooked	10	2 teaspoons

To one cup of clear broth add 80 gm. of tomatoes and 10 gm of onions cut fine. Cook for fifteen minutes. Season with salt and pepper.

When this soup is used, omit from the meal:

	Gm.	Approximate measure
Vegetable, 3 per cent	100	½ cup

3. *Vegetable Soup:*

	Gm	Approximate measure
Broth, clear		1 or 2 cups
Vegetable, 3 per cent, uncooked	50	¼ cup
Vegetable, 6 per cent, uncooked	25	⅛ cup

To the clear broth add 50 gm of tomato, celery, and cabbage, and 25 gm. of onions and carrots. Cook until the vegetables are tender. Season with salt and pepper.

When this soup is used, omit from the meal:

	Gm.	Approximate measure
Vegetable, 3 per cent.	100	½ cup

4 *Cream Soup:*

	Gm	Approximate measure
Cream	150	¾ cup
Vegetable, 3 per cent purée	30	⅛ cup

Add vegetable purée to hot cream. Season with salt and pepper.

When this soup is used, omit from the meal

	Gm	Approximate measure
Vegetable, 3 per cent	30	⅛ cup
Cream	150	¾ cup

5. *Oyster Stew:*

	Gm	Approximate measure
Milk	200	1 glass
Oysters	50	3 or 4
Butter	5	½ square

Season with salt and pepper.

When this stew is used, omit from the meal:

	Gm	Approximate measure
Vegetable, 5 per cent	65	⅓ cup
Milk	200	1 glass
Meat	15	½ serving

Hot Breads

1. *Popovers:*

	Gm	Approximate measure
Flour	20	3½ tablespoons (scant)
Eggs		2
Whipping cream	60	4 tablespoons
Salt		⅛ teaspoon

Beat the eggs thoroughly Add gradually, while beating, the flour with which the salt has been sifted. Add the cream slowly and beat until thoroughly mixed. Pour the mixture into hot buttered muffin tins. This recipe makes six popovers Bake in a very hot oven for five to eight minutes; then reduce the oven temperature, and continue the baking until the popovers are dry and crisp.

When one popover is used, omit from the meal:

	Gm.	Approximate measure
Vegetables, 3 per cent	100	½ cup
Butter	5	½ square

2. *Plain Muffins:*

	Gm.	Approximate measure
Egg	25	½ medium-sized
Milk	15	1 tablespoon
Butter	5	½ square
Flour	25	4½ tablespoons (scant)
Baking powder		½ teaspoon
Salt		¼ teaspoon

Sift the dry ingredients. Beat egg, add milk and melted butter. Add other ingredients and beat until smooth. Pour into greased muffin tins and bake in a moderate oven fifteen or twenty minutes.

This makes two muffins. When one muffin is used, omit from the meal.

	Gm	Approximate measure
Bread	20	1 thin slice
Meat	10	

3. *Blueberry Muffins.*

To the plain muffin recipe add 15 gm. of fresh blueberries.

When one muffin is used, omit from the meal:

	Gm.	Approximate measure
Bread	20	1 thin slice
Meat	10	
Fruit, *5 per cent*	20	1 rounding tablespoon

4. *Baking Powder Biscuits*

	Gm	Approximate measure
Flour	40	7 tablespoons (scant)
Butter	15	1 tablespoon
Baking powder		¾ teaspoon
Milk	40	3 tablespoons (scant)
Salt		⅓ teaspoon

Sift flour, baking powder and salt. Cut in the butter. Add the milk gradually. Knead just enough to make the dough smooth and shape into biscuits. Bake in a hot oven.

This makes two biscuits. When one biscuit is used, omit from the meal:

	Gm.	Approximate measure
Bread	30	1 slice
Butter	10	1 square

Note: This may be used as short cake by cutting in half and placing the fruit allowance between and also on top of the biscuit. Whipped cream may be used as garnish if the diet permits

5. *Corn Bread:*

	Gm	Approximate measure
Cornmeal	150	¾ cup
Flour	100	1 cup
Baking powder	15	5 teaspoons
Milk	200	1 cup
Egg		1
Salt		1 teaspoon

Mix dry ingredients. Add slightly beaten egg, then milk. Pour into buttered pan. Bake in hot oven. For one-twelfth of this recipe omit the following from your meal:

	Gm.	Approximate measure
Bread	30	1 slice
or		
Bread	20	1 thin slice
Fruit, 10 per cent	50	¼ cup

Protein Dishes

1. *Roast Pork and Apples*

	Gm.	Approximate measure
Roast pork, lean, cooked.	50	1 small serving
Apple	50	½ medium-sized
Butter	5	½ square
Salt and pepper to taste.		

Put 50 gm. of roast pork (cooked) into a small dish. Cover with 50 gm. of apple slices and 5 gm of butter. Add a small amount of water; cover and bake in a moderate oven about twenty minutes.

When this recipe is used, omit from the meal:

	Gm	Approximate measure
Fruit, 10 per cent	75	⅓ cup
Butter	5	½ square
Meat	50	1 average serving

2. *Beef Stew:*

	Gm.	Approximate measure
Meat, uncooked	60	1 average serving
Vegetables, 3 per cent, uncooked.	100	½ cup
Vegetables, 6 per cent, uncooked	50	¼ cup

To the uncooked meat add 2½ cups of boiling water and ¼ teaspoon of salt, and let simmer until tender. Remove meat from the water and add 100 gm. of cabbage, 25 gm. each of carrots and onions. Boil until the vegetables are tender. Add meat, heat again, and season with salt and pepper.

When this recipe is used, *omit* from the meal:

	Gm.	Approximate measure
Vegetable, 3 per cent	200	1 cup
Meat, cooked	50	1 average serving

3. *New England Boiled Dinner:*

	Gm.	Approximate measure
Meat, uncooked	60	1 average serving
Vegetables, 3 per cent, uncooked	100	½ cup
Vegetables, 6 per cent, uncooked	50	¼ cup
Vegetables, 15 per cent, uncooked	20	⅛ cup (scant)

To 60 gm. of corned beef add 3 cups of boiling water; simmer until meat is tender. Remove meat, add 100 gm. of cabbage, 50 gm. of carrots, and 15 gm. of parsnips. Boil until tender. Add meat, heat again, and season with salt and pepper.

When this recipe is used, omit from the meal:

	Gm.	Approximate measure
Vegetable, 3 per cent	100	½ cup
Fruit, 10 per cent	60	¼ cup
Meat	50	1 average serving

4. *Creamed Chicken with Asparagus:*

	Gm.	Approximate measure
Chicken, cooked	50	1 medium serving
Asparagus, cooked	100	½ cup
Cream	50	¼ cup

Cut the chicken into small pieces. Add the asparagus and to both add the heated cream. Heat again and season with salt and pepper. Mushrooms may be added in place of part of the asparagus.

When this recipe is used, omit from the meal:

	Gm	Approximate measure
Vegetable, 3 per cent	100	½ cup
Meat, lean	50	1 average serving
Cream	50	¼ cup

5. *Chicken Supreme:*

	Gm.	Approximate measure
Chicken, cooked	25	1 small serving
Egg		1
Milk	50	¼ cup
Celery	25	⅛ cup
Butter	5	½ square

Beat the egg slightly, add the chicken and celery (cut in small pieces), milk, salt and pepper. Put in a buttered mold, set in a pan of hot water and bake in a moderate oven until firm.

When this recipe is used, omit from the meal:

	Gm.	Approximate measure
Vegetable, 3 per cent	100	½ cup
Meat, lean	50	1 average serving
Butter	5	½ square

6. *Baked Fish, Spanish:*

	Gm	Approximate measure
Fish, uncooked	35	1 small serving
Water		½ cup
Tomatoes, cooked	80	½ cup (scant)
Onions, uncooked	10	2 teaspoons
Bacon, raw	10	1 strip

Place the fish in a small baking dish, add the water, tomato, onion, and the bacon which has been cut into small pieces Cover and bake in a moderate oven for twenty minutes. Season with salt and pepper.

When this recipe is used, omit from the meal.

	Gm	Approximate measure
Meat	25	½ average serving
Vegetable, 3 per cent	100	½ cup
Butter	5	½ square

Note: If desired, 5 gm. of butter may be used instead of the 10 gm. of raw bacon.

7. *Baked Egg and Tomato:*

	Gm	Approximate measure
Tomato, uncooked	100	1 small tomato
Egg		1
Butter	10	1 square

Scoop out the center of a raw tomato that weighs 100 gm Drop the egg into the tomato, cover with the scooped out pulp Add the butter, season with salt and pepper and bake for about fifteen minutes in a moderate oven.

When this recipe is used, omit from the meal:

	Gm	Approximate measure
Meat	25	½ average serving
Vegetable, 3 per cent	100	½ cup
Butter	10	1 square

8. *Poached Egg and Tomato:*

	Gm	Approximate measure
Tomato, cooked	100	½ cup
Egg		1

Put the cooked tomato in a small pan and heat. When it is boiling, drop the egg into the center. Remove the pan to a cooler part of the stove, cover and let stand until the egg white is firm and a film forms over the yolk. Season with salt and pepper and serve.

When this recipe is used, omit from the meal:

	Gm.	Approximate measure
Vegetable, 3 per cent	100	½ cup
Meat	25	½ average serving

9. *Egg with Tomato Sauce:*

	Gm.	Approximate measure
Egg, hard cooked		1
American cheese	20	1 inch cube
Tomato, cooked	100	½ cup
Butter	5	½ square

Mash egg yolk and mix with salt and pepper. Chop egg white fine and put into the bottom of a buttered baking dish. Then add the yolk. Cover with the cooked tomato and sprinkle the cheese on top. Bake long enough to melt the cheese.

When this recipe is used, omit from the meal:

	Gm.	Approximate measure
Meat	50	1 average serving
Vegetable, 3 per cent	100	½ cup
Butter	5	½ square

10. *Baked Egg with Cheese:*

	Gm.	Approximate measure
Egg		1
Cream	15	1 tablespoon
American cheese	20	1 inch cube
Butter	5	½ square
Salt and pepper to taste.		

Butter a small baking dish with the 5 gm. of butter. Add the egg, cream, and the finely grated cheese. Bake in a moderate oven until the cheese is melted.

When this recipe is used, omit from the meal:

	Gm.	Approximate measure
Meat	50	1 average serving
Butter	5	½ square
Cream (kind allowed on diet)	15	1 tablespoon

11. *Deviled Egg:*

	Gm.	Approximate measure
Egg, hard cooked		1
Vinegar		1 teaspoon
Mayonnaise	5	1 teaspoon
Mustard		a few grains
Paprika		a few grains
Salt and pepper		a few grains

Cut egg in half (lengthwise). Remove yolk and mix it thoroughly with seasonings and mayonnaise. Refill the white.

When this recipe is used, omit from the meal:

	Gm.	Approximate measure
Meat	25	½ average serving
Butter or mayonnaise	5	1 teaspoon

12. *Cottage Cheese Omelet.*

	Gm.	Approximate measure
Egg		1
Cottage cheese	35	1 heaping tablespoon
Butter	5	1 teaspoon

Add 2 teaspoons of water to the egg yolk and beat until thick and lemon colored. Then add the cheese, salt and pepper, and fold into the stiffly beaten egg white. Cook as an ordinary omelet.

When this recipe is used, omit from the meal.

	Gm.	Approximate measure
Meat	50	1 average serving
Vegetable, 5 per cent.	50	¼ cup

13 *Vegetable Omelet:*

	Gm.	Approximate measure
Egg		1
Vegetable, 5 per cent.	50	¼ cup
Water		1 tablespoon

Add water, salt and pepper to the egg yolk and beat until thick and lemon colored Then add the vegetable (either asparagus or tomato). Fold in the stiffly beaten egg white. Bake as an ordinary omelet in part of the butter allowed on the diet.

When this recipe is used, omit from the meal.

	Gm.	Approximate measure
Meat	25	½ average serving
Vegetable, 5 per cent	50	¼ cup

Vegetable Dishes

1. *Baked Cauliflower with Cheese:*

	Gm	Approximate measure
Cauliflower, cooked	100	½ cup
Tomato, cooked	100	½ cup
American cheese	20	1 inch cube
Butter	10	1 square
Season with salt and pepper.		

Butter a small baking dish with the 10 gm of butter. Add the cauliflower and tomato. Sprinkle the grated cheese on the top Bake in a moderate oven for twenty minutes. Cabbage may be substituted for the cauliflower.

When this recipe is used, omit from the meal:

	Gm.	Approximate measure
Vegetable, 3 per cent	200	1 cup
Meat	25	½ average serving
Butter	10	1 square

2. *Baked Onions:*

	Gm.	Approximate measure
Onions, uncooked	85	1 medium size
Ground meat, lean, uncooked	15	1 tablespoon
Milk	25	2 tablespoons (scant)
Butter	5	½ square

Parboil the onion and scrape out the insides leaving only the shell. Weigh shell and scrapings to 85 gm. Add meat, butter, salt and pepper. Return to the shell. Put in a casserole with milk, and bake until tender.

When this recipe is used, omit from the meal:

	Gm	Approximate measure
Meat	25	½ average serving
Vegetable, 3 per cent	200	1 cup

3. *Fried Tomatoes with Bacon:*

	Gm.	Approximate measure
Bacon, cooked	25	3 to 4 strips
Tomato, uncooked	100	½ cup

Fry the sliced tomato until tender in part of the butter allowance. Serve hot with the crisp bacon, after seasoning with salt and pepper.

When this recipe is used, omit from the meal:

	Gm	Approximate measure
Meat	25	½ average serving
Butter	10	1 square
Vegetable, 3 per cent	100	½ cup

4. *Squash Souffle:*

	Gm.	Approximate measure
Squash, cooked	75	⅜ cup
Milk	30	2 tablespoons
Egg		1
Butter	5	½ square
Salt and pepper		a few grains

Stir milk slowly into squash, add beaten egg yolk, salt and pepper. Fold in beaten egg white. Place in small, buttered baking dish and bake in a moderate oven until firm.

When this recipe is used, omit from the meal:

	Gm.	Approximate measure
Vegetable, 3 per cent	200	1 cup
Meat	25	½ average serving
Butter	5	½ square

5. *Cabbage au Gratin:*

	Gm	Approximate measure
Cabbage, cooked	65	⅓ cup
Meat (cooked and minced)	15	
Whipping cream, sour	30	2 tablespoons
Egg		1
American cheese, grated	10	
Salt and pepper		a few grains

Chop cabbage, add meat, cream, beaten egg, salt and pepper. Place in a buttered baking dish and sprinkle grated cheese on top Bake in a moderate oven until firm.

When this recipe is used, omit from the meal:

	Gm	Approximate measure
Vegetable, 3 per cent	100	½ cup
Meat	50	1 average serving
Butter	15	1½ squares

6. *Tomato Sauce:*

	Gm	Approximate measure
Tomatoes, cooked	100	½ cup
Butter	10	1 square
Flour	2	½ teaspoon

Melt butter, add flour and stir in tomatoes (strained) Cook for several minutes, stirring all the time and add salt and paprika Serve with meat dishes.

When this recipe is used, omit from the meal:

	Gm	Approximate measure
Vegetable, 3 per cent	150	¾ cup
Butter	10	1 square

Salads

1 *Cabbage and Nut Salad.*

	Gm	Approximate measure
Lettuce	20	2 or 3 leaves
Walnuts	10	4 halves
Cabbage, shredded	30	¼ cup

When this salad is used, omit from the meal:

	Gm	Approximate measure
Vegetable, 3 per cent	100	½ cup
Butter	5	½ square

2. *Raw Carrot and Nut Salad:*

	Gm	Approximate measure
Lettuce	20	2 or 3 leaves
Raw carrot, grated	20	⅛ cup
Walnuts	10	4 halves

When this salad is used, omit from the meal:

	Gm	Approximate measure
Vegetable, 3 per cent	100	½ cup
Butter	5	½ square

3. *Cottage Cheese Salad:*

	Gm.	Approximate measure
Lettuce	50	¼ small head
Cottage cheese	35	*1 heaping tablespoon*
Mayonnaise	5	1 teaspoon

When this salad is used, omit from the meal:

	Gm.	Approximate measure
Meat	25	½ average serving
Vegetable, 3 per cent	100	½ cup

4. *Pear and Nut Salad:*

	Gm.	Approximate measure
Lettuce	20	2 or 3 leaves
Pear	60	⅓ pear
Walnuts	10	4 halves

When this salad is used, omit from the meal:

	Gm	Approximate measure
Fruit, 10 per cent	100	½ cup
Butter	5	½ square

5. *Pear and Red Cherry Salad:*

	Gm	Approximate measure
Lettuce	20	2 or 3 leaves
Pear	50	¼ pear

One red cherry (canned without sugar) for garnish

When this salad is used, omit from the meal:

	Gm.	Approximate measure
Fruit, 10 per cent	50	¼ cup
Vegetable, 3 per cent	100	½ cup

6. *Tomato and Cottage Cheese Salad:*

	Gm	Approximate measure
Lettuce	20	2 or 3 leaves
Tomato	30	⅓ *medium-sized*
Cottage cheese	35	1 heaping tablespoon
Mayonnaise	5	1 level teaspoon

When this salad is used, omit from the meal:

	Gm	Approximate measure
Vegetable, 3 per cent	100	½ cup
Meat	25	½ average serving

7. Wilted Lettuce:

	Gm.	Approximate measure
Lettuce, shredded	50	½ cup
Bacon, cut fine	25	3 to 4 strips
Vinegar		2 teaspoons
Bacon fat	5	1 teaspoon

Cut crisp bacon into small pieces and add to heated bacon fat. Then add the vinegar, salt and pepper—cooking for a minute. Then pour over lettuce and serve at once.

When this salad is used, omit from the meal:

	Gm.	Approximate measure
Vegetable, 3 per cent	50	¼ cup
Meat	25	½ average serving
Butter	15	1½ squares

8. *Tomato Jelly Salad:*

	Gm.	Approximate measure
Tomato, cooked	80	½ cup (scant)
Onions, uncooked	10	2 teaspoons
Allspice		⅛ teaspoon
Cloves		⅛ teaspoon
Gelatin		1 teaspoon
Salt and pepper		a few grains

Cook the tomato, onions and spices for five minutes. Strain through a cheese cloth. Soak the gelatin in ¼ cup of cold water, and then add the hot tomato juice. Chill and serve.

When this salad is used, omit from the meal:

	Gm.	Approximate measure
Vegetable, 3 per cent	100	½ cup

9. *Pea, Pickle and Peanut:*

	Gm.	Approximate measure
Lettuce	20	2 or 3 leaves
Pickle, dill, cubed	25	⅛ cup
Peas	25	⅛ cup
Peanuts	10	10

When this salad is used, omit from the meal:

	Gm.	Approximate measure
Meat	25	½ average serving
Vegetable, 3 per cent	200	1 cup

10. *Tomato Stuffed with Shrimp and Celery.*

	Gm.	Approximate measure
Lettuce	20	2 or 3 leaves
Tomato	150	1 large
Celery, cubed	30	¼ cup
Shrimp	50	7 to 8
Mayonnaise	10	2 level teaspoons

When this salad is used, omit from the meal:

	Gm.	Approximate measure
Vegetable, 3 per cent	200	1 cup
Meat	50	1 average serving

11. *Chicken Salad:*

	Gm.	Approximate measure
Lettuce	20	2 or 3 leaves
Chicken, cubed	50	2 heaping tablespoons
Celery, cubed	20	¼ cup
Peas	15	1 tablespoon

When this salad is used, omit from the meal:

	Gm.	Approximate measure
Vegetable, 3 per cent	100	½ cup
Meat	50	1 average serving

12. *Salmon Salad:*

	Gm	Approximate measure
Lettuce	20	2 or 3 leaves
Salmon	50	2 heaping tablespoons
Pickle, dill, cubed	50	¼ cup
Celery, cubed	30	¼ cup

When this salad is used, omit from the meal:

	Gm	Approximate measure
Vegetable, 3 per cent	100	½ cup
Meat	50	1 average serving

13. *Egg and Cucumber Salad:*

	Gm	Approximate measure
Egg, hard cooked		1
Cucumber, uncooked	30	⅛ cup
Lettuce (or watercress)	20	2 or 3 leaves

Cut egg and cucumber in slices, arrange in a circle, alternating each and having the slices overlap each other. Fill the center with shredded lettuce or watercress.

When this salad is used, omit from the meal:

	Gm.	Approximate measure
Meat	25	½ average serving
Vegetable, 3 per cent	50	¼ cup

14. *Waldorf Salad:*

	Gm.	Approximate measure
Lettuce	20	2 or 3 leaves
Celery, cubed	30	¼ cup
Apple	70	⅔ medium-sized
Walnuts	10	4 halves

When this salad is used, omit from the meal:

	Gm	Approximate measure
Fruit, 10 per cent	100	½ cup
Vegetable, 3 per cent	100	½ cup
Butter	5	½ square

15. *Pineapple and Cheese Salad:*

	Gm.	Approximate measure
Lettuce	20	2 or 3 leaves
Pineapple (canned without sugar)	25	½ slice
Cheese	20	1 cubic inch (may be grated)

When this salad is used, omit from the meal:

	Gm.	Approximate measure
Meat	25	½ average serving
Vegetable, 3 per cent	100	½ cup

16. *Cabbage and Apple Salad:*

	Gm.	Approximate measure
Lettuce	20	2 or 3 leaves
Cabbage, shredded	50	½ cup
Apple, cut fine	50	¼ medium sized

When this salad is used, omit from the meal:

	Gm	Approximate measure
Vegetable, 5 per cent	100	½ cup

17. *Japanese Salad:*

	Gm	Approximate measure
Lettuce, shredded	20	2 or 3 leaves
Orange	40	¼ small sized
Tomato, fresh	25	¼ cup (scant)
Pineapple, fresh or canned without sugar	40	¼ cup (scant)
Cream (kind allowed on diet)	25	2 tablespoons (scant)

Mix and chill.

When this salad is used, omit from the meal:

	Gm.	Approximate measure
Fruit, 10 per cent	100	½ cup
Cream	25	2 tablespoons (scant)

Note: Walnuts may be added for variety to any of the salads; when 10 gm. is used, omit from the meal.

	Gm	Approximate measure
Vegetable, 3 per cent	50	¼ cup
Butter	5	½ square

18. *Cranberry Relish*

Grind 1 cup of cranberries and ½ a sectioned orange. Add the grated rind of ½ an orange and let stand one day. Add saccharin to taste.

If 20 gm., 2 teaspoons, of this relish is used, omit from the meal 20 gm. of 10 per cent fruit.

19. *Avocado Salad:*

If 50 gm. is used, omit 100 gm. of 3 per cent vegetable and 15 gm of butter.

Desserts

1. *Fruit Gelatin with Whipped Cream:*

	Gm.	*Approximate measure*
Orange, cubed	50	½ medium-sized
Banana, cubed	25	¼ medium-sized
Water		½ cup
Gelatin		½ teaspoon
Saccharin		¼ grain
Whipped cream	15	1 heaping tablespoon

Soak gelatin in one tablespoon of cold water. Add ½ cup of boiling water and allow to cool. Then add orange, banana and saccharin. When ready to serve place whipped cream on top.

When this dessert is used, omit from the meal:

	Gm	Approximate measure
Fruit, 10 per cent	100	½ cup
Butter	5	½ square

2. *Fruit Cup:*

	Gm.	Approximate measure
Orange, cubed	50	¼ cup
Grapefruit, cubed	50	¼ cup

When this dessert is used, omit from the meal:

	Gm.	Approximate measure
Fruit, 10 per cent	100	½ cup

3. *Orange and Strawberry Cup with Whipped Cream:*

	Gm.	Approximate measure
Orange	50	½ medium-sized
Strawberries, fresh	50	5 large
Whipped cream	15	1 heaping tablespoon

When this dessert is used, omit from the meal:

	Gm.	Approximate measure
Fruit, 10 per cent	100	½ cup
Butter	5	½ square

4. *Orange and Apple Cocktail:*

	Gm	Approximate measure
Orange, cubed	50	½ medium sized
Apple, cubed	30	¼ medium-sized
Lemon juice	5	1 teaspoon

When this dessert is used, omit from the meal:

	Gm.	Approximate measure
ruit, 10 per cent	100	½ cup

5. *Pineapple Bavarian Cream:*

	Gm.	Approximate measure
Pineapple, shredded (canned without sugar)	100	½ cup
Gelatin		½ teaspoon
Water, cold		2 tablespoons
Saccharin		¼ grain
Whipped cream	15	1 heaping tablespoon

Soak the gelatin in cold water. If there is some juice on the pineapple, heat it to boiling and pour over the gelatin to dissolve it. If there is no juice, dissolve the gelatin over hot water. Add the pineapple and when it is almost solid fold into it the whipped cream to which the saccharin has been added. Chill before serving.

When this dessert is used, omit from the meal:

	Gm.	Approximate measure
Fruit, 10 per cent	100	½ cup
Butter	5	½ square

6. *Plain Bavarian Cream:*

	Gm	Approximate measure
Egg		1
Milk	200	1 glass
Gelatin		1 teaspoon
Saccharin		½ grain
Vanilla		4 drops

Soak the gelatin in 2 tablespoons of cold water. Scald the milk in the top of a double boiler. Add it to the beaten egg and return to the double boiler, cooking the mixture until it coats the spoon (soft custard). Remove from the flame, add the gelatin and stir until it has completely dissolved, then add the saccharin and vanilla. When cool set it in refrigerator to chill.

This makes two desserts When one dessert is used, omit from the meal:

	Gm.	Approximate measure
Fruit, 10 per cent	50	¼ cup
Meat	15	½ average serving

For variety, 2 level teaspoons of cocoa may be added to the recipe. When this is done and one dessert is used, omit from the meal, in addition to the above:

	Gm.	Approximate measure
Vegetable, 5 per cent	35	¼ cup

7. *Plain Custard:*

	Gm.	Approximate measure
Egg		1
Milk	200	1 glass
Saccharin		½ grain
Vanilla		4 drops

Beat the egg and add the milk which has been scalded. Then add the saccharin and vanilla. Bake in a moderate oven for about a half hour. The custard cups should be set in a pan of water.

This makes two custards. When one custard is used, omit from the meal:

	Gm.	Approximate measure
Fruit, 10 per cent	50	½ cup
Meat	25	½ average serving

8. *Pumpkin Custard:*

	Gm.	Approximate measure
Egg		1
Milk	200	1 glass
Saccharin		¼ grain
Pumpkin	100	½ cup
Spices, as desired		½ teaspoon

Follow directions for baked custard, adding pumpkin to the beaten egg.

This makes two custards When one custard is used, omit from the meal:

	Gm.	Approximate measure
Fruit, 10 per cent	50	¼ cup
Meat	25	½ average serving

9. *Orange Mousse:*

	Gm.	Approximate measure
Whipped cream	50	½ cup
Orange	50	½ medium-sized
Saccharin		¼ grain

Add saccharin and orange, cut in cubes, to the whipped cream and freeze.

When this dessert is used, omit from the meal:

	Gm.	Approximate measure
Fruit, 10 per cent	50	¼ cup
Cream, 40 per cent.	50	¼ cup

10. *Ice Cream.*

	Gm.	Approximate measure
Egg		1
Cream, 20 per cent	60	⅓ cup
Vanilla		2 drops
Saccharin		¼ grain

Prepare as soft custard, cool and freeze.

When this dessert is used, omit from the meal:

	Gm.	Approximate measure
Egg		1
Vegetable, 5 per cent.	100	½ cup
Butter	15	1½ squares

11. *Orange Ice:*

	Gm	Approximate measure
Orange, lemon juice, and crushed pineapple	50	¼ cup
Mashed banana	25	⅛ cup
Egg		½ of the white
Gelatin		½ teaspoon
Saccharin		½ grain

When this dessert is used, omit from the meal:

	Gm.	Approximate measure
Fruit, 10 per cent.	100	½ cup

MISCELLANEOUS SUBSTITUTIONS

		Gm.	Approximate measure
1.	Cottage cheese	35	1 heaping tablespoon
	Butter	5	½ square

When this is used, omit from the meal:

	Gm.	Approximate measure
Meat	25	½ average serving
Vegetable, 5 per cent	50	¼ cup

2.	Oysters	100	6 to 7
	Butter	5	½ square

When this is used, omit from the meal:

	Gm.	Approximate measure
Meat	25	½ average serving
Vegetable, 5 per cent.	135	⅔ cup

3.	Pecans	10

When this is used, omit from the meal:

	Gm.	Approximate measure
Vegetable, 5 per cent	50	¼ cup
Butter	10	1 square

4.	Almonds	10

When this is used, omit from the meal:

	Gm.	Approximate measure
Bacon	10	2 strips

5.	Brazil nuts	10

When this is used, omit from the meal:

	Gm.	Approximate measure
Vegetable, 5 per cent.	25	⅛ cup
Butter	5	½ square

6. Peanuts 20

When this is used, omit from the meal:

	Gm.	Approximate
Vegetable, 3 per cent	35	⅙ cup
Butter	5	½ square
Meat	25	½ average se

7. Walnuts 10

When this is used, omit from the meal:

	Gm.	Approximate
Vegetable, 3 per cent...	50	¼ cup
Butter	5	½ square

8. Potato chips 20

When this is used, omit one of the following groups

	Gm.	Approximate
{ Fruit, 10 per cent.	100	½ cup
{ Butter	10	1 square
{ Bread	20	1 thin slice
{ Butter	10	1 square
{ Potato	50	½ average-size
{ Butter	10	1 square

9 Popcorn, popped and unbuttered 13 1 small bo

When this is used, omit from the meal:

	Gm.	Approximate m
Bread	20	1 thin slice
or		
Fruit, 10 per cent	100	½ cup

Butter may be subtracted from the diet and added to th corn.

10. Peanut butter .. .. 20 1 tablespoo

When this is used, omit from the meal:

	Gm.	Approximate m
Meat	25	½ average servi
Vegetable, 3 per cent...	35	⅙ cup
Butter	5	½ square

11. Cocoa .. . . 2 1 teaspoon

When this is used, omit from the meal:

	Gm.	Approximate me
Vegetable, 3 per cent....	35	⅙ cup

12. *French Toast:*

	Gm	*Approximate measure*
Bread	30	1 slice
Egg		1
Milk	15	1 tablespoon
Butter	10	1 square

To a well-beaten egg, add the milk and a few grains of salt. Dip bread into the mixture allowing all of it to be absorbed. Fry in the butter until golden brown.

When this recipe is used, omit from the meal:

	Gm.	Approximate measure
Bread	30	1 slice
Egg		1
Butter	10	1 square
Milk	15	1 tablespoon

6. Peanuts 20

When this is used, omit from the meal:

	Gm.	Approximate measure
Vegetable, 3 per cent	35	⅙ cup
Butter	5	½ square
Meat	25	½ average serving

7. Walnuts 10

When this is used, omit from the meal:

	Gm.	Approximate measure
Vegetable, 3 per cent	50	¼ cup
Butter	5	½ square

8. Potato chips 20

When this is used, omit one of the following groups of food:

	Gm	Approximate measure
{ Fruit, 10 per cent	100	½ cup
{ Butter	10	1 square
{ Bread	20	1 thin slice
{ Butter	10	1 square
{ Potato	50	½ average sized
{ Butter	10	1 square

9. Popcorn, popped and unbuttered 13 1 small bowl

When this is used, omit from the meal:

	Gm.	Approximate measure
Bread	20	1 thin slice
or		
Fruit, 10 per cent	100	½ cup

Butter may be subtracted from the diet and added to the popcorn.

10. Peanut butter ... . 20 1 tablespoon

When this is used, omit from the meal:

	Gm.	Approximate measure
Meat	25	½ average serving
Vegetable, 3 per cent	35	⅙ cup
Butter	5	½ square

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When this recipe is used, omit from the meal·

	Gm	Approximate measure
Bread	30	1 slice
Egg .		1
Butter	10	1 square
Milk	15	1 tablespoon

CHAPTER IX

OTHER THERAPEUTIC PROCEDURES IN DIABETES

In this chapter, measures other than diet and parenteral administration of insulin are to be evaluated, with apology for considering all of them together, since some, such as summer camps for diabetic children, are highly meritorious, others, such as hydrotherapy, are at worst innocuous, and still others have nothing to recommend them or are injurious or fraudulent. The important measures for the care of the feet of patients with occlusive vascular disease will receive attention, under the discussion of arteriosclerosis in Chapter XXII, and the treatment of other complications will be given in chapters dealing with complications.

CAMPS FOR DIABETIC CHILDREN

Dr. Priscilla White, believing that the diabetic child needs more frequent and longer periods of medical observation than usually are obtainable, spread the message of the diabetic summer camp. She opened the first of these "islands of safety" in 1925 and had such success that, in 1936, 106 girls were cared for at one camp in Massachusetts, seventy-five girls and boys at another, and still other children in smaller establishments in Vermont and New Hampshire. The example has been followed in several places. No project of social service could be more praiseworthy. *There is no group of children that will profit more from* attention than these little folk with diabetes.

In Philadelphia special arrangements made it possible to send diabetic children from the Metabolic Clinic of the University of Pennsylvania Hospital to the University Camp of the Christian Association, there to mingle with other children in all the activities of camp life. The diabetic children live apart in groups of ten, each group under the direction of a supervisor familiar with the special dietary requirements of these children, who knows how to administer insulin, to relieve reactions and to meet other emergencies. All other activities are directed by the regular

camp counselors. In them the diabetic children compete on equal terms with the other children which, as Richardson has suggested, is distinctly advantageous They win more than their share of honors and derive therefrom valuable self-confidence. Physicians make regular visits to camps such as these, and are on call when medical advice is required Such camps, when properly organized, also are a boon to parents who otherwise never obtain relief from the exacting responsibility of caring for a diabetic child.

HEALTH RESORTS AND MINERAL WATERS

What the summer camp provides for the diabetic child the health resort could offer the adult. Unfortunately, in America, health resorts have not been established for those who cannot afford to pay well, and most of the spas available to the rich are commercialized to a degree that makes them anything but "islands of safety" for patients with diabetes. In Europe, where balneology is more respected, outstanding authorities on diabetes, although frequently questioning the reputed virtues of the waters themselves, find that the sojourn of patients at spas, such as Karlsbad, Neuenahr, Marienbad and others, is often distinctly beneficial. The benefits are for milder cases. Patients with diabetes difficult to control do better in their homes, and those with complications associated with the development of acidosis, require hospital care far more than any mineral water.[1]

EXERCISE

Patients with well controlled and uncomplicated diabetes thrive on exercise. With it the requirement for insulin is di-

[1] The scientific study of the effects of medicinal muds and waters, because of commercial considerations, has not been disinterested It is to be hoped that the extensive research, which now is under way in the Central Institute for the Science of Health Resorts in Moscow, will provide more dependable information as to what can be accomplished for diabetes and other diseases by these natural methods of treatment This institute is not the only place in Russia where such study has been undertaken extensively Sigerist wrote that in Leningrad the Institute of Physiotherapy has a special balneological service, and that institutes of hydrology and climatology have been established in Kharkov, Odessa, Tiflis, Tashkent, Erivan, Batum, Yalta and other places, each of them with laboratories and sanatoria devoted to research There can be no doubt, he said, that through its health resorts the Soviet Union today is forging one of the most powerful weapons for the restoration of the health of its people

minished and, if the dose of insulin is suitably adjusted to avoid reactions, they feel better. On the other hand, in uncontrolled diabetes exercise elevates the blood sugar and intensifies the wasting characteristics of the disease. Richardson and Case showed this most conclusively, finding that a standard form of exercise markedly lowered the blood sugar in mild cases, in which the fasting blood sugar level was between a normal value and 0.175 gm. per 100 c.c., but progressively elevated it in cases in which the fasting values were between 0.176 and 0.300 gm. per 100 c.c. In the severe cases a minute dose of insulin given intravenously, which was without noticeable effect before a period of rest, would markedly lower the blood sugar level when given before a period of exercise. The comparison of the effect of exercise, with and without insulin, in mild and severe diabetes suggested to him that in mild diabetes the chief disturbance in the metabolism of carbohydrate is an inadequate, or inadequately available, reserve of glycogen in muscle and liver, while in severe cases there is more or less complete inability to convert the dextrose of the blood to the needs of the tissues.

ORAL INSULIN

Efforts to protect insulin from the action of the enzymes of the gastro-intestinal tract in order to enable administration by mouth in the treatment of diabetes heretofore have been unsuccessful. That insulin is able to pass the intestinal barrier has been demonstrated, however, by numerous investigators who used isolated loops of bowel. Murlin and associates also have presented evidence of activity when insulin, in preparations containing hexylresorcinol, was given perorally to depancreatized dogs. Clinical results with a different preparation have been reported by Lasch and Schönbrunner. These writers found that acid organic dyes, such as Congo red, trypan red and others, will protect insulin from disintegration by pepsin, and that individual basic dyes, among them malachite green and rhodemine, similarly will protect it against trypsin. The addition of saponin to insulin had been found by others to increase absorption in Thiry fistulas and with tablets containing saponin, trypan red, malachite green and dry insulin, Lasch and Schönbrunner conducted experiments with results that are impressive. Clinical trial of this preparation was

undertaken in several German clinics, among them Eppinger's in Vienna. Forty diabetic patients were given the tablets for limited periods in amounts representing doses of insulin varying from 60 to 300 units daily, and data regarding eight of these are included in Lasch and Schönbrunner's report. The diabetes of most of the eight was of considerable severity; for its control 45 to 60 units of insulin injected subcutaneously were necessary. Doses of oral insulin to be equally effective were from two to four times as large. The necessary inclusion of saponin limits the usefulness of the preparation and some doubt as to the safety of long-continued administration of the dyes named may be expressed. No serious side effects were observed, but nausea, vomiting and diarrhea, referable exclusively to the amount of saponin, were encountered Some patients proved to be more sensitive to the disturbing effects of saponin than others. Two patients were treated for six and one patient for eleven months without any disagreeable symptoms. The report is conservative. The authors claimed to have proved conclusively that insulin is absorbed and active when given by mouth, according to the procedure described, but they reserved judgment on the clinical usefulness of the preparation until it had received wider clinical trial.

DIABETIC NOSTRUMS

The statement from "Queries and Minor Notes," the Journal of the American Medical Association, which follows should serve as a warning for those who because of dislike for the hypodermic injection of insulin turn to preparations of reputed effectiveness by mouth:

"No oral insulin [preparation] has been accepted by the Council on Pharmacy and Chemistry. . . Over eleven years ago, The Journal in discussing 'Enterocap Oralsulin' (Dec. 4, 1926, p 1935), pointed out the lack of evidence for the efficiency of orally administered preparations of insulin and pancreas. . . . No new evidence has been found to necessitate a revision of the statement published at that time. Recently the federal authorities charged with the enforcement of the Food and Drugs Act seized a shipment of Enterocap Oralsulin and declared the product adulterated and misbranded. According to the government report, examination showed that the preparation contained no

insulin and that the labeling bore false and fraudulent representations regarding the curative or therapeutic effects of the product. (Notice of Judgment 27373, Food and Drug Administration, U. S. Department of Agriculture, issued December, 1937). No products of Lafayette Pharmacal, Inc., stand accepted by the Council on Pharmacy and Chemistry."

The campaign which has been conducted by Federal agencies and the American Medical Association against diabetic nostrums has eliminated many of those of the past, but new ones crop up like weeds. It is to be hoped that adequate appropriations by Congress will make it possible to enforce the much more satisfactory acts passed in 1938 to regulate the advertising and sale of foods, drugs and cosmetics. A favorite ingredient of so-called diabetic cures has been a diuretic drug, such as wild carrot (Queen Anne's lace). In other cases the promoter seems to depend on the effectiveness of the accompanying diet directions. The spectacular testimonials distributed with such nostrums often have been written by innocent victims whose death notices were published before the testimonials appeared.

GUANIDINE DERIVATIVES

Not in the category of nostrums, but of limited value and possessing injurious properties, are the guanidine derivatives, synthaline (deca-methylene-diguanidine) and neosynthaline (duodeca-methylene-diguanidine). They never have been accepted by the Council on Pharmacy and Chemistry of the American Medical Association, but are used rather widely in Europe. Our clinical experience with them (Wilder and Allan, 1928) confirmed their reputed hypoglycemic effect, but showed this to be limited in most cases to that obtainable with relatively few units of insulin, that larger doses could not be given without provoking symptoms of toxicity, that acidosis was not effectively prevented and that patients with diabetes of mild intensity were not improved even when the amount of the drug given caused the concentration of blood sugar to fall. In a case of juvenile diabetes, synthaline provoked severe vomiting and dangerous acidosis.[a]

[a] A recent study of synthaline which completely invalidates claims for its usefulness in the treatment of diabetes was reported by Schuler.

PLANT EXTRACTS

Extracts of a great variety of plants, dispensed usually in the form of decoctions, have long been used as folk remedies in the treatment of diabetes. It has been supposed that in many cases they inhibit glycosuria by inducing nausea or diarrhea. Collip, and later Best and Scott, however, found sugar-depressing principles in extracts of a number of plants, and myrtillin, in which Allen later took an interest was unquestionably active when administered to depancreatized dogs. Myrtillin was an extract of blueberry leaf Clinical trial of it in one case of severe diabetes at the clinic disclosed some steadying influence on the blood sugar. In two other cases, in which insulin was being used, the dosage of insulin could be reduced not more than 5 units; in ten other cases, the results were entirely negative.[3]

OPIUM

A drug which in former days was much used in the treatment of diabetes is opium According to Hogler and Zell opiates in small doses depress blood sugar values but in larger doses raise them. The same, according to Krause and Marx, applies to the use of opium in cases of diabetes

ALCOHOL

The use of alcohol in diabetes is no longer an important problem That it has some antidiabetic effect has been shown, but this is too feeble compared with that of insulin to be of practical significance. Dependence on alcohol as a food which cannot be converted to sugar has been made unnecessary by insulin, and the stomachic and tonic values of alcohol are of no greater importance

[3] For numerous references to substances of this nature the reader may consult the monograph on insulin by Hill and Howitt Plants which are reputed to have antidiabetic properties also occupy a place of some importance with the Chinese Among those studied by King Li Pin, Shih Yuan-Kao and Li-Teng Pang the most active hypoglycemic property was found in Rehmannia glutinosa When an alcoholic extract of the root of this plant was injected into rabbits in a dose of 2 c c, representing 4 gm of fresh root, the average blood sugar values over five hours were as follows before injection, 0 085 gm per 100 c c, one hour after injection, 0 053, two hours, 0 049, three hours, 0 046, four hours, 0 043, and five hours, 0 044 Another reported plant extract with hypoglycemic potency is one from the roots of a shrub called Devil's club (Fatsia horrida) which, it is reported, has been used for centuries by the Indians of British Columbia (Large and Brocklesby).

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to the patient whose diabetes is managed properly than to normal persons. On the other hand there is no contraindication in diabetes to the consumption of moderate quantities of alcoholic beverages. These conclusions are based on a review of the subject which I prepared in 1932 for Emerson's "Alcohol and man."

THE VITAMIN B COMPLEX

It is not impossible that some of the hypoglycemic effects of decoctions and extracts of vegetable material are due to the presence in such preparations of one or several of the factors of the vitamin B complex. That vitamin B plays some rôle in carbohydrate metabolism was suspected by Funk and von Schönborn, because their pioneer studies demonstrated that feeding carbohydrate would aggravate the symptoms of beriberi, and that limiting the intake of starches and sugars was beneficial in this avitaminosis. The observation has been widely confirmed.

Funk's vitamin B now is known to be a complex of nutritional factors of which several, including thiamin (vitamin B_1) and riboflavin (vitamin B_2) have been isolated and synthesized Thiamin has to do with the removal from the blood and tissues of lactic and pyruvic acids, also probably of methylglyoxal, all three of these substances being intermediates in the metabolism of dextrose. This naturally suggests that the disturbed metabolism of diabetes might be affected favorably by administering this vitamin. Vorhaus and associates, Martin and Schroeder, have claimed that it was; von Drigalski has reported differently. Tislowitz, giving large doses of thiamin to normal dogs, observed less elevation of the blood sugar by dextrose and increased sensitivity to insulin associated with slowing of the pulse. The slow pulse suggested to him that the effect of the vitamin might be mediated through the central nervous system and the vagus. Riboflavin also was found by Schroeder to lower the level of the blood sugar in diabetes.

It is not improbable that the several factors of the vitamin B complex are synergistic and that the complex as a whole may have effects greater than those of any of its components taken separately. Several reports have appeared to indicate that concentrates of the complex, such as rice polishings and brewers' yeast, may favorably affect the tolerance of diabetic patients. Also,

the blood of patients with diabetes has been found by Magyar to be less effective than normal blood in relieving the symptoms of beriberi when fed to pigeons and young rats suffering from this avitaminosis. The substance missing in the diabetic blood was not determined. To judge from unpublished observations in our laboratories it probably is not vitamin B_1.

In future monographs on diabetes these few paragraphs may need to be replaced by an important chapter. At present the evidence of value in diabetes from therapeutic doses of the vitamin B complex, or any of its constituents, is conflicting but suggestive. The diabetic organism probably requires more of the vitamin B complex than easily is obtained in a mixed diet. If diets high in white flour and sugar are prescribed, the danger of deficiency is increased, and with such diets it probably is wise to supplement the intake of the entire vitamin B complex by giving brewers' yeast. Doses of thiamin or riboflavin, in excess of the amounts of these obtainable in well planned diets, have not been therapeutically effective, except in cases in which the intake of these substances previously has been deficient, but much work under way in this field and conclusions must be withheld.[*]

EXTRACTS OF DUODENAL MUCOSA

The administration by mouth of a crude preparation of secretin was found by Takács to lower the levels of blood sugar of normal men and of patients with diabetes. The effect was attributed to stimulation of the islands of Langerhans. Macallum made similar observations with extracts of duodenal mucosa, and La Barre showed that the in vitro digestion of such preparations with weak solutions of pepsin suppressed their succagogue activity and left their hypoglycemic action intact. Such preparations are without effect in depancreatized dogs. Laughton and Macallum and also Heller made similar observations and Duncan and his associates and La Barre have announced favorable therapeutic results with such preparations in cases of severe and mild diabetes

[*] Monauni has presented evidence that the fluctuation of the blood sugar can be stabilized by administering large doses of thiamin. Jordan, writing from Breslau, believed that vitamin B is a true and physiologically significant peroral antidiabetic remedy. He insisted that those who have obtained poor results from its use have failed either because they used only vitamin B_1 or were content to use bakers' yeast, which is less rich than brewers' yeast, not only in B_1 but also in the accompanying factors of the vitamin B complex, including glutathione.

The weakness in these observations, from the standpoint of practical therapeutics, has been the inconstancy of the preparations obtainable. Some extracts undoubtedly have hypoglycemic activity; others, made the same way, apparently are inert.

SALTS OF SODIUM AND POTASSIUM

The existence of a reciprocal relationship between the metabolism of sodium chloride and that of dextrose has been suggested by observations, such as the lower than normal levels of chloride in the blood of patients with diabetic acidosis. In consequence Glass and Beiless were led to inject sodium chloride in cases of diabetes. They observed that the values for blood sugar fell with regularity. Similar results, although less striking, were obtained when salt was given by mouth. A vagotonic action was suggested in explanation.

A more careful study of this subject was made by McQuarrie, Thompson and associates. A child with diabetes who was possessed of an inordinate craving for table salt, three other diabetic patients and one normal child, all in the age group between thirteen and fifteen years, were given pure sodium choride by mouth, in doses of from 1 to 2 gm. per kilogram of body weight per day The degree of a pre-existent glycosuria of the diabetic patients was diminished markedly and the sugar content of the blood was brought to considerably lower levels. Also the respiratory quotients, ketonuria and nitrogen balances were improved. Sodium bicarbonate and sodium citrate, when given in such amounts that the value for sodium was equivalent to that obtained on administration of sodium chloride, had similar although less marked effects. Potassium salts were found to exert an opposite action. A diet high in potassium either prevented or greatly lessened the effect of the sodium, and potassium chloride in doses of from 10 to 20 gm. daily, together with a diet low in sodium, significantly increased glycosuria. MacLean added the observation that treatment of a patient presenting a relative insensitivity to insulin with sodium chloride was particularly effective. In his case the requirement for insulin steadily declined from 115 to 55 units a day Subsequently we have treated successfully a number of patients having a relative insensitivity to insulin with satisfying results. In such cases the diet should be made low in potassium,

like the diet that Sister Mary Victor has planned for use in the treatment of Addison's disease.

SUCCINIC ACID

MacKay, Sherrill and Barnes, and others cited by them have been unable to corroborate in any degree the findings of Koranyi and Szent-Györgyi concerning the desirable therapeutic effect of succinic acid on human diabetes; namely, that ketosis may be reduced or controlled by this compound. In a normal fasting person they found succinic acid to be no more antiketogenic than an equivalent amount of glucose, to which succinic acid is converted in the phlorhizinized and probably also in the normal organism

SPECIFIC THERAPY

Specific therapy, defined by Dorland as treatment by a remedy which acts directly against the cause of disease, is as yet but little available in diabetes. *Therapia morbi*, in the strict sense of the term, would involve restoration of fundamentally adequate insular tissue by heterotransplantation of pancreas. Thus far this has not been performed successfully, although Stone of Baltimore had some success in transplanting pancreatic cells after adapting them to the new environment by previous culture in graduated dilutions of the serum of the host. However, depending on how much etiologic significance is to be placed on the activity of the physiologic antagonists to insulin, surgical and other measures designed to diminish the degree of this antagonism may be considered under etiologic therapy.

Surgical treatment of diabetes.[5]—Mannsfeld working with normal dogs found that the tolerance for sugar could be increased by isolating the tail of the pancreas. De Takats and his associates confirmed both this observation and that made previously by Bensley and Herxheimer, that the islands in the distal part of the pancreas underwent hypertrophy after ligation of the pancreatic duct In their series of five dogs when the pancreas was divided with the electric cautery and then wrapped in omentum, flattened dextrose tolerance curves and excessive hypoglycemia were pro-

[5] The literature contains a number of references to a moderate alleviation of experimental diabetes obtained by ligating the parotid ducts There is not enough promise in this procedure, however, to justify its further exploration

duced. Improved dextrose tolerance also was demonstrable by means of continuous injections of dextrose at timed rates. In three of the five animals the increased tolerance to sugar persisted for several months; in two it receded after a month or two. Finally, this operation was performed in two carefully selected cases of juvenile diabetes, with results that were similar to those obtained in animals (de Takats and Wilder). In each case a gradual increase in dextrose tolerance occurred at approximately the fourth month; this did not persist at its highest level but gradually diminished.[*]

The principal reason for the failure to produce enduring improvement of dextrose tolerance by ligation of the pancreas was thought to be advancing sclerosis, which at first affected only the acini but later interfered with the blood supply to the islands. The possible presence of some hormonal or nervous inhibition to pancreatic function, which originally may have led to the internal failure and after the operation produced exhaustion of the newly formed island tissue was also considered.

These observations suggested another line of attack, and led de Takats and Cuthbert to study the effect of celiac ganglionectomy. They reported that when the celiac gland of normal dogs was removed a rise in dextrose tolerance could be demonstrated, associated with increased sensitivity to insulin. The data were interpreted as indicating that the exclusion of the nerve impulses from the celiac ganglion either brings about an increased production of insulin, possibly by increasing the blood supply of the pancreas, or accomplishes a reduction in the requirement for insulin. Bilateral denervation of the adrenals or bilateral section of the splanchnic nerves gave identical results, and the last of these procedures was selected for trial in two cases of diabetes. In the first case, that of an eighteen-year-old girl with unstable diabetes and moderate insensitivity to insulin, an abrupt change was obtained in the dextrose-insulin ratio from 2 5:1 to 5:1, together with other marked general improvement; both persisted

[*] In one of these cases the requirement for insulin immediately after operation was markedly diminished, only to rise again to its previous level in a few days
pancreatic vessels, the result
ates, studying the influence
tervention provoked hyper-
secretion of insulin

cond case, in which the patient was not insensitive to no benefit was obtained.[7]

al and other treatment directed at insulin antagonists — erations by which theoretically there is hope of allevi- intensity of diabetes involve resection of glands of secretion with activity opposed to that of the pancreas adrenalectomy is obviously out of the question, although n surgeon, Donati, performed adrenal denervations, as ne American surgeon also has done, with some unfor- sults[8]

physectomy has been performed in one case reported by r and co-workers. The patient was a fifteen-year-old boy ere diabetes of seven years' duration, complicated by ry tuberculosis. The operation was carried out success- l the insulin requirement subsequently fell from 150 or s to 70 or 80 units a day. A tendency to severe hypo- reaction was not corrected, and some months later the lied of tuberculosis. It is of special interest from the al point of view of those who believe in the etiologic ce of the pituitary in diabetes, that the pituitary in this carefully studied and revealed no abnormalities.

rthyroidism decreases the sensitivity to insulin and hypo- sm increases it This subject is to receive more attention ffice it here to comment on the effect of total ablation yroid in two cases of diabetes in which this operation has formed. In one case, reported by Foster, Pemberton and patient, a white man twenty-six years of age, volunteered

Takats, Fenn and Trump have described two tests for differentiating abetes By the first the sensitivity of the patient to an intravenous injec- 01 units of insulin per kilogram of body weight is determined, by the

with sensitivity to ergot are the only ones that offer hope of benefit by the splanchnic nerves

off described the development and fatal outcome of Addison's disease suprarenal denervation for diabetes mellitus A similar case in which l denervation had been performed elsewhere later came to our attention lder, and Cragg). At necropsy degeneration of both suprarenal glands l This change seemed to be attributable to interference with the blood the time of the denervation

to undergo the operation in the hope of securing some improvement of his unusually severe, but uncomplicated diabetes of eleven years' duration. A morphologically normal thyroid gland was removed, and following the operation the basal metabolic rate fell to less than —30 per cent. The tolerance for carbohydrate rose concurrently so that a previous requirement of 45 units of insulin ultimately was lowered to 8 or 12 units. The diet before and after operation consisted of 103 gm. of carbohydrate, 59 gm of protein and 183 gm. of fat. Despite the improved tolerance the benefits obtained were not sufficient to justify recommendation of the procedure as a treatment for diabetes. Restricted dieting and some insulin continued to be necessary, and the patient complained that sensitiveness to cold and lack of endurance were so disturbing that the advantage of the improvement in tolerance for carbohydrate was not appreciated. In another case of total ablation of the thyroid, reported by Rudy, Blumgart and Berlin, the diabetes was complicated by tuberculosis.

Attempts to suppress the activity of the suprarenal glands by roentgen treatment of these organs has not been successful. On the other hand, Hutton and Merle noted improvement of diabetes after intensive irradiation of the pituitary. In the case described by Merle, as well as in one of Rathery and Froment, the patients before treatment were resistant to insulin. In Merle's case the glycosuria was more marked at the time of menstruation and some endocrine antagonist to insulin was suspected. The pituitary was irradiated from both sides in eight treatments, two each week. The total dose of roentgen rays amounted to approximately one-third the sterilizing dose for the ovary. The output of sugar was less after the treatment, even though no insulin was used, than it had been previously with large doses of insulin. Cannavo also is reported to have irradiated the region of the hypophysis and thereby to have overcome abnormal resistance to insulin. On the other hand, Selle, Westra and Johnson failed entirely to confirm the observation of Hutton and those of Barnes and associates (1935), who reported improvement of the diabetes of depancreatized dogs after roentgen irradiation of the pituitary. In five to seven depancreatized dogs the sugar content of blood drawn before breakfast was not lowered by irradiation of the pituitary, and

there was no indication that the severity of the symptoms was diminished. The doses administered were so massive that one would not dare to employ them in treating a patient, and the degree of damage from such treatment to nerve structures and other hormones of the hypophysis is conjectural. The opinion was expressed by Selle, Westra and Johnson that before treatment of diabetes by irradiation can be endorsed the rationale for this treatment must be better.

Another method of dampening the action of the pituitary is to administer large doses of the products of the end organs, such as the ovaries which normally are dependent on the pituitary for stimulation Some benefit has been obtained in the acromegalic symptoms of patients with acromegaly, by giving daily injections of estrin-in-oil (Kirklin and Wilder), and when large doses of corticosterone were administered to rats, the adrenotropic action of the pituitary was suppressed (Ingle). Barnes and his associates (1933) found that giving estrogenic substance to normal female dogs prevented all but mild glycosuria after pancreatectomy. Soskin and his co-workers, attempting a clinical application of thi principle, obtained similar results on administering estrogenic substance to diabetic patients. I previously have referred to a case of insulin resistance in a woman with menopausal symptoms, in which the dose of insulin was lowered from 100 to 50 units a day by such treatment Unfortunately experience has been less favorable with other cases.

A blood sugar depressing effect of parathyroid extract has been reported by Zunz and La Barre Olmer and Paillas have confirmed this. The effect, however, does not appear to the latter investigators as a direct one, for the reason that injection intravenously into an isolated extremity caused no change.

Woodyatt gave an extract of the anterior lobe of the hypophysis to diabetic patients, with the purpose of creating resistance to its activity (antihormone effect). The glycosuria increased during the course of the injection, but after the high dosage was interrupted, improvement occurred in the tolerance for carbohydrate, comparable to that which follows removal of the pituitary. This interesting and promising therapeutic suggestion ought to be put to further trial.

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CHAPTER X

ACIDOSIS AND COMA IN DIABETES

Certain complications in diabetes are feared, not for themselves alone, but because by them diabetes is intensified and thereby coma is provoked. Acidosis in diabetes may result from neglect of treatment but with equal frequency an infection or the shock of an operation is responsible. Thus, although itself a dreaded complication, diabetic acidosis and coma can hardly be considered apart from those complications which may precipitate acidosis, especially infection, trauma and operations. These topics will receive attention in succeeding chapters.

HISTORICAL ACCOUNT

Coma with fatal outcome was so frequent an occurrence in diabetes that it early attracted the attention of clinicians Von Stosch's description in 1820 is readily recognizable, and in 1854 both Marsh and von Dusch commented on the unusual characteristics of this type of coma Von Dusch raised the question whether it could be related to uremia but he decided that it could not Then Petters, in 1857, in a fatal case with a strong odor suggestive of chloroform, identified acetone in the blood and urine, and Gerhardt introduced his iron-chloride test for diacetic acid in urine containing acetone Finally, in 1874, Kussmaul wrote his classical description of the characteristic hyperpnea since then known as Kussmaul's respiration: "There is nothing to suggest that the air on its way to or from the lungs has even the least obstruction to overcome. The thorax expands fully in all directions, complete inspiration is followed by just as complete expiration. Stasis of blood in the veins of the neck is absent, likewise any cyanosis This 'grosse Atmung' furthermore is usually accelerated. The contrast of the general weakness with the strength of the respiratory movements is one of the most impressive features of the clinical picture."

The discovery of the nature of acidosis by Naunyn and his pupils, in the clinic in Konigsburg, between 1878 and 1880, represented one of the most brilliant contributions of clinical medicine to general physiology The story is told in Naunyn's autobiography. Liberally translated, but with no important omissions, the account is as follows.

In 1878 Walthers, in Schmiedeberg's laboratory, discovered that injection of inorganic acids stimulated excretion of ammonia by the kidneys. The subject of urinary ammonia was one with which Naunyn already was interested, and Walthers' work prompted a systematic investigation in the medical clinic in Konigsburg to determine whether the output of ammonia in disease would provide some insight into the processes of intermediary metabolism—a hope later brilliantly realized in diabetic acidosis.

Tedious preliminaries were necessary before methods of analysis suitable for clinical use could be developed; then a series of experiments was required to establish that the quantitative dependence of urinary ammonia on acidification held good for man as well as for other animals At last all was ready for the principal problem, the excretion of ammonia in disease A pupil, Halerworden, to whom Naunyn proposed the topic as a thesis, himself chose first to investigate diabetes mellitus, and fortune provided that the first case was one in which there was very severe acidosis Halerworden found in it the "Kolossale Ammoniakscheidung" of 10 gm. a day.

It could scarcely be doubted that this tremendously exaggerated output of ammonia signified a correspondingly enormous excretion of acid, but first it was necessary to discover whether the acid was one of unusual origin or merely represented excessive formation of acids, such as phosphoric and sulfuric acids, which normally are derived from protein The latter possibility at first seemed more likely, because in Halerworden's patient protein catabolism was appreciably accelerated Stadelmann, who in the meantime became Naunyn's clinical assistant, undertook to find the answer It was necessary to determine quantitatively all of the known acids and corresponding bases in the urine The task was tremendous; nevertheless, it was accomplished, and a huge acid deficit remaining indicated the presence in large quantities of an organic acid thus far unknown

Next came the problem of identifying the unknown acid It would not crystallize An accident brought both assistance and confusion Stadelmann heated the syrupy mass without having any particular purpose in mind, added sulfuric acid and obtained crystalline *alpha crotonic* acid Naunyn objected at once that the action of sulfuric acid might have modified the original material, but Stadelmann, convinced that he had the correct answer, refused to listen, and sometime later, without Naunyn's approval, published his results and his interpretations

Naunyn by this time had the problem well in hand. In all specimens of urine in which the questionable syrupy acid had been found aceto-acetic acid and acetone were also present, and it seemed not unlikely that some single mother substance existed from which on the one hand crotonic acid could be formed, and on the other, these two acetone bodies It was then that Minkowski became Stadelmann's successor. Naunyn, when he gave the problem to Minkowski, explained that he thought that Stadelmann was mistaken, and suggested a search through chemical textbooks for an acid from which all three substances, crotonic acid, acetone and aceto-acetic acid migh
be derived The very next day Minkowski found a book (Gorup-Besane
which readily showed that the acid they were seeking could be oxybutyric ac
They also learned how best to isolate the substance, and at long last obtaine
in a purified form Analytically it was *beta-hydroxybutyric* acid, *l* beta
droxybutyric acid as later was demonstrated by Külz. By this means the th
of diabetic acidosis was established "Mit jener Arbeit Stadelmann's wa
Lehre von der diabetischen Acidose fest begründet. Durch den Fun
Oxybuttersäure war sie in der Hauptsache ausgestaltet. Es war ein gew
Arbeitsfeld, das sich uns da eröffnete und es hat bis heute seine F
barkeit bewahrt."

Diabetic coma is the end result of uncontrolled severe di
The term is unfortunate because consciousness occasionall

mobilizing the various mechanisms possessed by the body for ridding itself of excessive acid The condition then is one of ketosis with compensated acidosis in which large amounts of ammonia are found in the urine. It was encountered in the era before insulin in practically all cases of severe diabetes True acidosis, in the sense of diminished alkali reserve, may accompany such ketosis, but when it does it frequently is not severe.

A condition more dangerous than the chronic one described is brought about when the rate of formation of ketonic acids is rapid, as occurs not infrequently at the onset of the diabetes of childhood, or in any case of severe diabetes when treatment with insulin is interrupted Then time is not allowed for compensatory adjustments, the mechanisms for maintaining the neutrality of the body are overwhelmed, and the alkali reserve of the blood is quickly depleted. The course, in cases of severe uncompensated acidosis, unless treatment is instituted, is rapidly progressive, with early fatal termination In this condition the respiration is stimulated, urine is passed in large amounts, and by these means, as well as by vomiting the tissues soon are dehydrated and depleted of sodium chloride and other salts Soon afterward the volume of the blood is diminished, the circulation fails, renal excretion is depressed and the body temperature falls The carbon dioxide combining power of the plasma may reach the extraordinarily low value of 2 volumes per cent, it usually dips below 35 volumes per cent before respiratory symptoms appear. The blood is concentrated, but the values for the chloride and sodium in the plasma are depressed. The blood fats increase at times to very high values, the value for nonprotein nitrogen rises, and very high values for sugar are obtained Leukocytosis develops; counts of 20,000 are not infrequent and one of more than 60,000 has been seen unassociated with evident infection Consciousness is dulled early and deep coma usually is established for some time before death; however consciousness in some cases is no more than dulled until the end Not infrequently death has occurred after the clinical abnormalities have been corrected by appropriate treatment.

Experimental evidence (Wilder, 1917) led to considering aceto-acetic (diacetic) acid rather than beta-hydroxybutyric acid as the mother substance of the ketone bodies. In severe states of

tained to the end in fatal cases of acidosis, whereas more often it may be lost when the degree of acidosis, as judged by the carbon dioxide combining power of the plasma, is less extreme. What sometimes is implied by the term is an arbitrary value for the carbon dioxide combining power of the plasma, this serving as a criterion for classification of cases. Joslin and Root, for example, adopted the value 20 volumes per 100 c.c. as the upper limit in cases of "coma," because in pre-insulin days recovery could be obtained in most cases of acidosis when the value was above this figure. In our clinic, as Baker has written, the value 25 volumes per 100 c.c. has been adopted, because in several cases unconsciousness has accompanied values for carbon dioxide combining power between 20 and 25 volumes per 100 c.c.

ABNORMAL PHYSIOLOGY IN DIABETIC ACIDOSIS

By the fanciful description of Rosenfeld "fats burn in the fire of the carbohydrates." Fats in metabolism are hydrolyzed; their fatty acids thus are separated from combination with glycerin Other fatty acids arise from protein when amino-acids are deaminized. *Beta* oxidation then occurs, according to the theory of Knoop, whereby each fatty acid attacked successively at the carbon atom next to the carboxyl group and disintegrating, two links at a time, is converted into a chain only four carbons in length—butyric acid ($CH_3\,CH_2\,CH_2\,COOH$). To this point the metabolism of fat proceeds with or without the "fire of carbohydrate," but at this point, when the organism is inadequately supplied with carbohydrate or, as in severe diabetes, is unable to utilize what it has, the process hesitates. Beta oxidation again occurs, but instead of again breaking the chain, it gives rise to ketonic acids also four carbon atoms long. The ketone bodies—as Woodyatt descriptively has put it—are like soot from a smoking lamp—products of incomplete combustion. Aceto-acetic acid (diacetic acid) apparently is the first to form ($CH_3\,CO\,CH_2\,COOH$). This in turn gives rise, to a small extent, to acetone and to a greater extent to beta-hydroxybutyric acid ($CH_3\,CH_2\,CHOH\,COOH$).

The disturbed metabolism of fatty acid, in an organism unable properly to utilize carbohydrate, may develop slowly, so that accumulation of ketonic acids occurs gradually and time is given for

mobilizing the various mechanisms possessed by the body for ridding itself of excessive acid. The condition then is one of ketosis with compensated acidosis in which large amounts of ammonia are found in the urine. It was encountered in the era before insulin in practically all cases of severe diabetes. True acidosis, in the sense of diminished alkali reserve, may accompany such ketosis, but when it does it frequently is not severe.

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ketosis four times as much beta-hydroxybutyric acid may be found in the urine as aceto-acetic acid, and the idea has been entertained by several investigators that the conversion of aceto-acetic acid to beta-hydroxybutyric acid represents to some extent a process of detoxification. Additional evidence of this has been provided by Schneider and Droller, who found that a state "resembling diabetic coma" could be induced in rabbits by long continued intravenous infusion of the sodium salt of aceto-acetic acid, but not by injection of comparable amounts of the sodium salt of beta-hydroxybutyric acid. Injection of hydrochloric acid produced coma less readily, and only at lower values for the alkali reserve. From this it was suggested that the coma of diabetic acidosis is due less to the acidosis than to a specific intoxication by the aceto-acetic anion.

An important study of the metabolism of patients with diabetic acidosis has been reported by Engel, with the suggestion that failure of the cortex of the adrenal glands has a determining part in the deaths of patients. As coma threatens, the concentration of chloride and sodium in the plasma falls abruptly; indeed repeated determination of the chloride in the urine offers a sure and convenient method of controlling treatment. In diabetic acidosis, as in the crisis of Addison's disease, a rich supply of hypertonic salt solution and solution of sodium bicarbonate is demanded. It also has been emphasized by Engel that the diet of young and asthenic diabetic patients should never be low in sodium chloride.

INCIDENCE OF DIABETIC ACIDOSIS

The percentage of all diabetic deaths from acidosis, in statistics of Marble, cited by Joslin, for the years 1930 to 1936, was 6.1. For the pre-insulin, Naunyn period, 1898 to 1914, it was 63.7. The improvement obviously is attributable to the better treatment made possible by the discovery of insulin. Fine as this is, still better results should be expected, as has been shown in Joslin and Marble's comparable statistics of the mortality among physicians who have diabetes. In the period 1922 to 1936, only 3.3 per cent of deaths of diabetic physicians came from coma. The doctors, as Joslin has implied, take better care of themselves than they are able to take of their patients.

accelerated but also deepened (Kussmaul's breathing), the situation is critical.

The early treatment of diabetic acidosis is lifesaving, but care must be exercised, since a hasty decision to inject insulin may have serious consequences in coma of other than diabetic origin or when coma is due to hypoglycemia. The differential diagnosis of diabetic coma and insulin coma is considered elsewhere (p 102). The hyperpnea of the former, the strong fruity odor of acetone of the breath, the red lips and cheeks, the dehydrated skin and tongue and the soft, sunken eyeballs, constitute a picture which is not difficult to recognize. However, sometimes the physician is called to treat a patient who has been overtreated with insulin for diabetic acidosis and has passed out of this state, through a short period of consciousness, into the coma of hypoglycemia and, under such circumstances, certain of the signs of diabetic coma, such as a dry skin, soft eyeballs and acetone breath, persist.

PROGNOSIS

The immediate prognosis in severe diabetic acidosis is affected by: (1) the age of the patient, (2) the degree of unconsciousness—this, as well as the duration of unconsciousness before the institution of treatment is of more significance prognostically than the value for blood sugar or the degree of depletion of the alkali reserve, (3) the presence or absence of infection, and (4) the normality of the heart and kidneys.

The mortality at The Mayo Clinic from coma among patients in the first four decades of life, was 4 per cent; among those in the next four decades it was 40 per cent. This experience is much in accord with that reported by Marble and Joslin. Long duration of severe acidosis and the degree of unconsciousness are indexes of gravity Ten patients in the series of Mayo Clinic cases reported by Baker had been completely unconscious for more than twelve hours. Of this group only three survived. He found less correlation between mortality and the degree of depression of the carbon dioxide combining power of the plasma or the degree of hyperglycemia. However, Dillon and Dyer, who reported twenty-five cases in which the values for the blood sugar were more than 1.000 gm. per 100 c.c., observed that the mortality was more than twice as high in cases in which values exceeded 0.700 gm. per 100

c.c. as it was in cases in which they were less than 0.400 gm. per 100 c.c. That the outcome will be unfavorably affected by accompanying infection or cardiorenal disease is self evident. In five of the seventeen cases reported by Baker in which death occurred, fulminating infection precipitated the acidosis and accounted for the deaths; in four of the fatal cases cardiorenal disease was pre-existent. A grave complication is cardiovascular collapse, with attending anuria and uremia. A tubular nephritis caused by toxic injury of the epithelial cells is a frequent finding in diabetic acidosis, and it may further impair renal function. This is responsible for the showers of casts ("coma casts") frequently found in the urine in acidosis.

Rabinowitch, Fowler and Bensley (1939), investigating the mortalities for diabetic "coma" from four large clinics, found them not to be comparable because of the many variables which influence mortality from coma. They therefore proposed, for future use in evaluating different methods of treatment, grading coma on the basis of a "severity index." In the calculation of this a numerical value was assigned to each of the various factors for which, in their experience, a positive correlation existed These data showed that exception could be taken to any of the variables when used alone, but that the combined use of all of those shown in Table 5 provided information of superior prognostic value.

The ultimate prognosis in cases of diabetic coma would be satisfactory, in our experience, were it not for "repeaters." Patients who because of carelessness have suffered one attack are likely to have others for the same reason The patients in 50 per cent of ninety-nine cases in the series reported by Baker had other attacks either before or after their initial visit to the clinic, and in many instances death resulted in one of the later attacks We have not observed that patients who have undergone an attack of coma are unusually susceptible to tuberculosis, as reported by Root.

Unexplained deaths.—In a number of cases of diabetic coma control of the chemical abnormalities of the blood has been obtained but the patients have died. In some of these cases consciousness was restored and the patient has seemed to be on the road to recovery; then he collapsed. The cause of such deaths

is unexplained. Usually they are sudden deaths, suggesting pulmonary embolism or acute dilatation of the heart, but at necropsy no emboli can be found and the heart is not greatly dilated. In some such cases the heart stops before the respirations, although in other cases respiratory failure occurs first.

Cerebral lesions are found at necropsy in uncomplicated cases of diabetic acidosis, and I have long supposed that in some fatal cases respiratory failure was a result of respiratory exhaustion by overstimulation of respiratory centers in the medulla. Myocardial damage also is evident in some cases. However, both of these

TABLE 3
CALCULATION OF SEVERITY INDEX*

Factor	Rating 1	2	3	4	5
Age (years)	-15	16-30	31-50	51-70	71+
Duration of coma (hours)	-12	13-24	25-36	37-48	49+
Degree of unconsciousness	Drowsy	Semi-conscious	Unconscious but response to pain†	Completely unconscious	
Coffee ground vomitus			Present		
Infection			Present		
Blood pressure (systolic)	89-80	79-70	69-60	59-30	29-
Plasma carbon dioxide combining power	19-16	15-12	11- 8	7- 4	3-
Blood urea nitrogen (mg per 100 c c)	21-30	31-40	41-50	51-60	61+
Associated conditions‡	Very mild	Mild	Moderately severe	Severe	Very severe

Clinical stage	Severity index
Very mild	- 5
Mild	6-10
Moderately severe	11-15
Severe	16-20
Very severe	21+

* From Rabinowitch, Fowler and Bensley (1939)
† Elicited by touching conjunctivæ
‡ Include only acute conditions capable of causing death independent of the coma.

findings are inconstant. In eight cases in which the brain was examined at necropsy Dillon, Riggs and Dyer noted capillary dilatation, pericapillary edema and degeneration of ganglion cells.

The most satisfactory study of the electrocardiogram of patients in diabetic coma is that reported by Bellet and Dyer. The findings of others have been conflicting, but Bellet and Dyer, who obtained serial electrocardiograms, observed significant abnormalities in every one of seventeen cases of coma and less marked abnormalities in six cases of precoma. The principal

alterations consisted of lengthening of the Q-T interval, depression of the S-T interval and inversion of T waves. In all but three cases the abnormalities eventually disappeared; however, the greatest alteration was observed not during coma but about twenty-four hours later when the patient was recovering, and in one case the final return to normal was delayed for a month.

The transient nature of these electrocardiographic abnormalities led to the suggestion of functional rather than structural damage to the myocardium, the change being slowly reversible. Any one or several factors may be responsible: the acidosis *per se*, the loss from the blood of ions of sodium and chloride, the loss of blood volume, the dehydration or the breakdown of tissue (muscle) protein.[1] That the measures resorted to in the treatment of acidosis are not sometimes responsible for fatalities is worthy of consideration. Insulin itself is probably blameless, unless enough is given to provoke hypoglycemia, but too sudden a restoration of the blood volume may have unfavorable effects and abrupt changes in osmotic relationships resulting from rapid corrections of severe hyperglycemia may not be harmless.

PREVENTION OF COMA

Diabetic acidosis is avoidable and for coma to develop is usually inexcusable. Deaths from coma would be almost eliminated if all diabetic patients would adhere to the following rules

[1] That tissue protein is depleted in diabetic acidosis is evidenced by accompanying azoturia and azotemia. Dillon and Dyer found a better correlation of mortality in diabetic coma with degree of azotemia than with degree of hyperglycemia or degree of depression of carbon dioxide combining power. In their 268 cases of coma the mortality in cases in which the value for blood urea nitrogen was 0.020 gm. per 100 c.c. or less was 22 per cent, whereas in those cases in which the value exceeded [illegible] value for blood urea [illegible] 021 gm. per 100 c.c., [illegible] tion between the de[illegible] ey divided their patients into "conscious" and "unconscious" groups, according to whether it was possible to arouse the patient enough to answer "yes" or "no" to some simple question, and found the mortality among the conscious group to be 28 per cent and that among the unconscious group 81 per cent. In their uncomplicated cases only 5.4 per cent of the "conscious" patients died.

Owens and Rochwern of the University of Cincinnati likewise placed great emphasis on the degree of unconsciousness of the patient. They found the carbon dioxide combining capacity of the plasma to be of no practical prognostic significance. Their mortality in cases in which young patients were conscious or semi-conscious was 18.2 per cent, whereas for unconscious patients the mortality ranged from 47.5 for patients under twenty years of age to 85.7 per cent for older patients.

1. Never neglect daily testing of urine and step up the doses of insulin to prevent gross glycosuria (see p. 93).

2. Never omit insulin because of inability to take food, unless the urine is sugar free.

3. Always inform surgeon, dentist and chiropodist of the presence of diabetes before operations, extractions of teeth and chiropody.

4. Keep up resistance to infection by avoiding severe fatigue, either physical or mental, and securing recreation and regular sleep.

5. Avoid close contact with persons who have colds or other contagious diseases. Keep away from theaters and other assemblies in times of epidemics.

6. Consult your physician early for the treatment of any infection you may acquire, with or without fever; with or without any infection call him urgently if any two of the following group of symptoms develop:

(a) Unexplained weakness and drowsiness.
(b) Loss of appetite and nausea, with or without vomiting.
(c) Unusual pain in abdomen, legs or back.
(d) Dry skin and tongue with increased thirst.
(e) Increased respiration with fruity acetone breath.
(f) Persistent gross glycosuria with positive urine tests for diacetic acid.

TREATMENT OF DIABETIC COMA

In order of relative immediate importance, the measures employed in treating diabetic acidosis are:

1. Rest and heat.
2. Insulin.
3. Water and salt.
4. Alkali.
5. Gastric lavage (rectal lavage).
6. Cardiac stimulation.
7. Urinary catheterization.
8. Dextrose.
9. Continued treatment.

The rationale of each of these will be considered in order, but will be given the standing orders by which we are guided a patient with severe acidosis is admitted to the hospital.

Standing orders for treatment of coma.[2]—These are as follows:

1. Place the patient in a single room in bed between blankets. Place hot water bottles close to the body and thighs, avoiding the legs and feet. Call a special nurse and a special laboratory technician; if possible have them on hand when the patient arrives *Call the consultant.*

2. Inject insulin. For an adult give from 50 to 100 units of protamine-zinc insulin in one hypodermic site and from 20 to 40 units of unmodified insulin in another; for a child give relatively smaller doses. The size and frequency of subsequent doses will depend on clinical discriminations and the results of examination of blood and urine. Usually, additional doses of unmodified insulin are to be given at intervals of three hours; see paragraph 10.

3. Collect blood from vein. Fill a 20 c.c. centrifuge tube containing sodium oxalate for determination of the values for sugar, chloride, urea and carbon dioxide combining power. Repeat the examination of the blood for sugar and carbon dioxide combining power not less frequently than once every three hours until the patient is out of danger. Secure additional blood for grouping in case transfusion of blood is required later.

4. Start intravenous injection of physiologic salt solution at a rate not exceeding 20 c.c. per minute. The same needle inserted for collecting blood should be used without withdrawal for this injection. Give *not less than* 30 c.c. per kilogram of body weight (14 c.c. per pound) in the first six hours, 15 c.c. per kilo-

[2] The procedure outlined by these standing orders is based on an experience represented by nearly 250 cases in which patients either were unconscious on admission to the hospital or the carbon dioxide combining power of the blood plasma was 25 volumes per cent, or less. Observations based on 108 of these cases were reported in 1936 by my assistant Dr Baker In three instances in this series patients were admitted unconscious yet with values for carbon dioxide combining power of 25 volumes per cent. In six of the seventeen fatal cases the value was more than 20. Had the patients in these cases been omitted the mortality rate for the series would have been 14.9 per cent instead of 15.7

Acidosis of the degree mentioned has been found in only 1.6 per cent of all patients with diabetes admitted to The Mayo Clinic. This incidence is low when compared to that encountered by Joslin in Boston (2.8) and John in Cleveland (4.0). The explanation presumably is our situation in a small town. In the year 1937, 71 per cent or 876 of 1185 diabetic patients registered from states other than Minnesota, and only 5 per cent were from the city of Rochester Patients with severe acidosis obviously cannot apply for treatment in a distant city, but by the same token those who do attempt to reach the clinic frequently arrive after many hours in conditions of extreme severity

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should be administered intravenously at three-hour intervals. The solution of dextrose may be added to what physiologic salt solution is being administered by vein, but not to a solution containing either sodium bicarbonate or compound solution of iodine (Lugol's solution).

9. Determine and record the blood pressure hourly. If the systolic pressure falls below 80 mm of mercury, give the hypertonic salt solution mentioned in paragraph 7 and arrange for an immediate infusion of blood or acacia.

10 Continue periodic examinations of blood and urine and administration of insulin at intervals of two or three hours. Until the consultant orders otherwise, give 15 units of regular insulin for a grade 4 reaction to Benedict's test for sugar in the urine, 10 units for a grade 3 reaction, 5 units for a grade 2 reaction, and if there is no reaction administer 10 gm of dextrose.

11. When the patient is seen in his home he should be transported to a hospital, but the first administration of insulin should be given before starting, and if the journey will take more than two hours the physician should accompany the patient and give what other treatment is possible in transit. Telephone the hospital so that arrangements can be made for immediate attention on arrival.

12 Record all laboratory reports and clinical observations on the "Diabetic coma chart" (Fig. 12).

Rationale of therapeutic measures—The rationale of the measures named for the treatment of severe diabetic acidosis is as follows

1. Rest and heat.—The patient with severe acidosis is utilizing no carbohydrate and drawing on endogenous supplies of fat and protein for his energy requirement. By rest in bed the requirement for calories is reduced, and thereby the catalysis of ketogenic precursors is diminished. The continuous attention of a nurse is desirable, not only for the assistance she can be to the physician, but also to keep the patient quiet.

The fall in body temperature that accompanies other shock-like states also is encountered in diabetic acidosis, and is to be combated with warm, not heavy, blankets, and hot water bottles Heat also may help to lower the rate of energy production, and thereby contribute beneficially. In using the hot water bottles the

gram (7 c.c. per pound) in the second six hours, and 15 c.c. per kilogram (7 c.c. per pound) *in the next twelve hours. For 60 kg.* (132 pounds) the volumes will be 1800 c.c., 900 c.c. and 900 c.c. When consciousness is not seriously impaired and the patient is not vomiting, the administration can be by mouth or by duodenal tube.

5. Prepare, or order prepared by the following directions, a 5 per cent solution of sodium bicarbonate. Boil 1000 c.c. of freshly distilled water three minutes; remove from flame and dissolve in it 50 gm. of clean sodium bicarbonate. The solution must not be boiled. When it is ready aspirate the gastric contents, wash the stomach, using 500 c.c. of the bicarbonate solution for the purpose, and leave about 100 c.c. of the solution in the stomach. By this time the report, from the laboratory, of the *carbon dioxide combining power of the plasma will have arrived.* If the value is less than 20 volumes per 100 c.c., add the remaining 500 c.c. of the 5 per cent solution of sodium bicarbonate to the salt solution running into the vein.

6. Look for complications which may be responsible for the patient's acidosis—infection, hyperthyroidism. If infection is found, consider measures for its removal or treatment; if any suspicion of hyperthyroidism exists, give compound solution of iodine *(Lugol's solution)* (1 c.c. added to *what fluid is being* given by vein or duodenal tube each six hours).

7. Collect separately for analysis every specimen of urine voided. If micturition is impeded, catheterize the bladder once every three hours, exercising special precautions to avoid infection. Examine each specimen for sugar and aceto-acetic acid. It is to be remembered that the effect of frequently repeated injections of insulin may be cumulative, and that it is safer, until the patient has regained consciousness, not to give enough insulin to suppress glycosuria completely. In cases in which anuria results from circulatory collapse, slowly inject intravenously 60 c.c. of 10 per cent solution of sodium chloride.

8. After two or three hours start administering small doses of sugar. If the patient is not nauseated, this can be given by mouth or duodenal tube with orange juice or as 10 per cent solution of dextrose in amounts of 150 c.c. every two or three hours; otherwise 150 c.c. *of a sterile 10 per cent solution of* dextrose

1931. Occasionally, heroic doses have been given. Before control was obtained and consciousness was restored in one case in which there was circulatory collapse 980 units were required. In two cases reported by Root and Riseman more than 1300 units were used.[3]

Kepler and Wilbur and I expressed the opinion, based on observation of patients with diabetic coma treated since 1936, that considerable benefit attends the use of some protamine-zinc insulin at the beginning of treatment. The dose has not exceeded 100 units, and obviously in a case of severe coma this amount will not meet all requirements. Furthermore, in an emergency where every moment counts, the retarded action of protamine-zinc insulin is a disadvantage. However, when used as we use it at the clinic, to supplement more vigorous treatment with unmodified insulin, protamine-zinc insulin has diminished the size of the doses of unmodified insulin necessary and has permitted lengthening the intervals between injections of unmodified insulin

Injection of unmodified insulin intravenously usually is restricted to cases in which coma is complicated by circulatory collapse, when absorption from subcutaneous deposits may be retarded. *A more rapid insulin effect may be obtained by this* means, but I am not convinced of the wisdom of rapid lowering of the concentration of blood sugar, thereby provoking abrupt changes in osmotic relationships It has seemed to me that some deaths may be laid to this cause.[4] Furthermore, the principal damage in diabetic acidosis is done, not by hyperglycemia, but by dehydration and acidosis, and quicker control of these can be obtained by administering water, salt and alkali than by insulin

3. Water and salt.—The dehydration induced by the forma-

[3] [illegible]

is disadvantageous

danger of burning the skin and the special sensitiveness of the extremities of patients with arteriosclerosis should be held in mind.

2. Insulin.—Everyone with experience in the treatment of *acidosis* agrees that insulin must be given as early as possible in all cases of diabetic acidosis and that the dose required is increased by acidosis. On the other hand, in early cases of diabetes in which the patients are children, in all cases in which the patients are *undernourished and when the attack of coma is a first attack,* care must be exercised to avoid overdosage. In a completely

DIABETIC COMA CHART

Date and hour	Time since adm., hrs.	Urine			Blood			Insulin		Fluid			B P mm. of Hg	Remarks
		Vol., c.c.	Sugar gm. per 100 c.c.	Acetone +	Sugar gm. per 100 c.c.	CO_2 vol %	Urea, mg per 100 c.c.	P units	R units	Vein, c.c.	Subcutaneous, c.c.	Oral, c.c.		

Fig 12.—Form of the diabetic coma chart Summarize data every twelve hours total volumes of fluid given, total excretions Doses of insulin given *intravenously are to be indicated with letters IV* after the numbers of units In column for "Remarks" record all other items of treatment, such as gastric lavage, enemas, and so forth, also type of fluid given, and all other medication

unconscious seven-year-old child with a carbon dioxide combining power of the plasma of only 9 volumes per 100 c c., consciousness was restored and other symptoms were relieved by the administration of a total amount of only 28 units, and in another child, aged eleven years with a carbon dioxide combining power of only 2 (!) *volumes per 100 c c., 70 units of insulin sufficed.* In 1931 our average dose for the first twenty-four hours was 148 units, but in 1923 it was only 67 units. *The relatively* smaller requirement in 1923 probably is explained by the fact that diabetic patients on admission in that year usually were undernourished. Our average dose today probably exceeds what it was in

of alkali as he believes, and furthermore, others have done as well using alkali, although admittedly with fewer cases. Bowen and Hekimian for instance, gave alkali in 76 per cent of eighty-one cases in which the carbon dioxide combining power did not exceed 15 volumes per 100 c.c. of plasma, and the mortality was 12.4 per cent. Baker, reporting from The Mayo Clinic, found that we had given alkali in 31 per cent of 108 cases, in doses of from 25 to 50 gm., and that our mortality was little greater than that at the Deaconess Hospital. Furthermore, patients reaching Rochester in coma have had to come from a distance, and therefore frequently arrive after having been in acidosis for prognostically unfavorable lengths of time.

In the pre-insulin era treatment of acidosis depended almost entirely on the use of alkali, with results that were very poor. The disrepute of alkali, therefore, dates from that era. The doses then given frequently exceeded 100 gm.[a] In cases in which patients have been treated with insulin, water and salt alone, I have seen deaths occur from respiratory paralysis, which I believe could have been avoided by earlier control of acidosis. The terrific overstimulation of the respiratory centers in severe acidosis is manifest in the hyperpnea observed. A little alkali—the injection slowly of 25 gm. of sodium bicarbonate in 5 per cent solution—usually corrects hyperpnea almost instantly. Insulin takes more time to do so, and time is precious.

Furthermore, as Starr and Fitz were first to observe, an amount of organic acid, not ketonic, and later shown by Himwich to be

[a] The observation of Mosenthal, that removing acids from the blood by the use of alkali could injure vulnerable kidneys, was based on pre-insulin therapy when large doses of alkali were given. The observation that administering alkali is followed by increased excretion of ketone, and that ketosis can be demonstrated in the urine of normal persons receiving sodium bicarbonate led Haldane and his co-workers to conclude that alkali interfered with combustion of carbohydrate. With this I disagree, as I have repeatedly demonstrated, in the case of nonacidotic patients receiving insulin, that the requirement for insulin is lowered slightly by administering small doses of sodium bicarbonate. On the evening of January 31, 1937 a patient was admitted stuporous and vomiting to one of our wards. A physician, still living in the Naunyn age and apparently without knowledge of insulin, had treated the diabetic acidosis with soda, giving 10 or 15 gm. hourly for about twenty hours. Hyperpnea had been relieved, but not the nausea or

tion in the body of organic acids is accompanied by an *enormous* loss of electrolytes. In consequence the volume of the circulating blood is diminished, and the effectiveness of the heart is impaired. These abnormalities demand early correction, which usually is provided by giving in the first six hours from 30 to 40 c.c. of physiologic salt solution per kilogram of body weight (13 to 18 c.c. per pound), followed by an equal amount administered in the next eighteen hours. The fluid usually is first administered by vein, later by mouth, if consciousness returns and nausea and *vomiting have ceased* This amount of fluid may not compensate entirely for what has been lost, but the wisdom of more rapid rehydration is doubtful.[5]

4. Alkali.—Joslin's insistence that alkali is disadvantageous in diabetic coma is known to everyone. Pointing with just pride to his very low mortality figures, he demanded that others must do as well, giving alkali, to establish the validity of such usage. His excellent results, however, are in large part explained by the prompt and energetic treatment and by the meticulous care that patients receive from him and his assistants in the New England Deaconess Hospital, expert as they have become as a result of an enormous experience with diabetic acidosis. Joslin's results, therefore, may not be as acceptable as evidence against the use

[5] Much discussion was aroused by Root and Riseman, who reported giving 12,000 c c of liquid in one case of coma in the first eleven hours of treatment, and 11,660 c c. in another Among the questions raised was the amount of fluid that needs replacement The authors named found 5000 c c of salt solution ample in most of their cases but emphasized that these two cases constituted exceptions and required vastly more aggressive treatment A painstaking study of dehydration is that of Coller, whose estimates of possible water loss in acidosis were as follows 1. For loss in twenty four hours by vaporization from skin and lungs, 1000 to 1500 c.c; if there is fever or hyperthyroidism, this would be increased to 2500 c c. 2 For loss through urine, 1500 c c, making a total daily requirement for replacement of from 2500 to 4000 c c A patient who has been in diabetic acidosis for twenty-four hours probably has lost a maximum through the lungs, more than 1500 c c. through the urine, and frequently more by vomiting *Signs of severe dehydration,* such as scanty urine, dry skin, dry tongue and sunken eyes, did not appear, he [illegible] had been lost in fluid, and therefore [illegible] ms, [illegible] ter [illegible] att. [illegible] on the basis of observations on dogs dehydrated by means of hypertonic solution of dextrose, concluded that full rehydration in diabetic acidosis required replacement of not more than 5 per cent of the body weight and stated that symptoms disappear before this amount is given His advice was to give fluid in coma by mouth, if possible, otherwise as physiologic salt solution subcutaneously at a rate not in excess of 1 5 c c per kilogram per hour.

the way for administering fluid by mouth. I also have supposed that removing the gastric contents contributed in a small way to the removal of acid—both hydrochloric and organic. The use of a 5 per cent solution of sodium bicarbonate for the subsequent lavage, and leaving 100 or 200 c c. of this in the stomach, has seemed to have a soothing effect.

The cleansing enema is not an immediate necessity, although by this means the bowel is prepared for later administration of fluid by proctoclysis

6. Cardiac stimulation —The utility of cardiac stimulation is debatable. However, I shall continue to give digitalis early in a form suitable for subcutaneous or intramuscular injection, and in a dose, for adults, of 2 cat units each four hours for three or four doses. This use of relatively small doses of digitalis to increase cardiac tone, in conditions in which there is danger of acute dilatation, was recommended by my former chief, Dr Frank Billings. On the other hand, large, so-called digitalizing doses of digitalis, in acute toxic states, are generally out of favor.

For circulatory collapse the continuous injection of physiologic salt solution is probably as effective as anything short of transfusion of blood. Transfusion of blood certainly is indicated, as has been emphasized by Peters, Kydd and Eisenman, but is not always immediately available The addition of 1 mg of epinephrine to 1500 c c. of physiologic salt solution for injection intravenously has been recommended by Labbé and Boulin. I have used ephedrine subcutaneously, camphor in oil and caffeine sodium benzoate. In cases of anuria I have resorted to the intravenous injection of 60 c c. of 10 per cent solution of sodium chloride as recommended by Joslin The danger of injury to the kidneys from this dose of such hypertonic solutions of salt is minimal, if we may judge from pathologic material obtained from human beings in whom such injections have been made before death.[7]

7 Urinary catheterization —Unless forced to do so, Joslin prefers not to catheterize patients for fear of introducing infec-

[7] See also the experiments on dogs of Lindberg, Wald and Barker who injected 50 c c of a 10 per cent solution of sodium chloride Dog 224 received ten such injections on success[illegible]

lactic acid, at least in part, is excreted in some cases of coma in amounts exceeding the ketone acids. The administration of insulin cannot accomplish the removal of this. In a few of our cases reported by Baker ketonuria was absent or minimal and in several others, although ketone formation was controlled after giving insulin, the carbon dioxide combining power of the plasma remained at low levels until it was later corrected by administering alkali.

The patient in the following case (case 79 in Baker's series) recovered. I am convinced he would not have done so without alkali. The unconscious patient, a boy aged eleven years, was admitted to the hospital at 5:00 a m. The value for sugar was 0.380 gm. per 100 c.c. of blood, and that for carbon dioxide combining power of the plasma was only 2 volumes per cent. The urine reacted only faintly with the nitroprusside reagent, and the odor of acetone was minimal. Six hours later, although sufficient insulin had been administered to lower the value for blood sugar to normal, that for the carbon dioxide combining power of the plasma had increased only to 12 volumes per cent. Within the next few hours more insulin was given, together with a 5 per cent solution of dextrose. This also failed to increase the alkali reserve, to suppress hyperpnea or to restore consciousness, although the level of blood sugar by then had been practically normal for ten hours. Finally, 300 c.c. of a 5 per cent solution of sodium bicarbonate was given intravenously, and within an hour the hyperpnea was relieved and consciousness was returning.

Another reason for giving alkali is based on the observation of Atchley and others that in acidosis more base is lost than inorganic acid In this respect the condition resembles that encountered in the crisis of Addison's disease, where the use of alkaline salts of sodium, in addition to sodium chloride, is highly beneficial.

5. Gastric and rectal lavage.—Dilatation of the stomach is a frequent accompaniment of diabetic coma, and of itself constitutes a menace. It causes embarrassment to cardiac and respiratory function as well as pain, nausea and vomiting. Burgess, Scott and Ivy found in dogs that prolonged distention of the stomach by means of a balloon filled with water caused death within periods of from twenty-six to seventy hours. Lavage of the stomach frequently will terminate pre-existing nausea and pave

plained of fatigue and generalized aching In the evening nausea and vomiting began and soon she was unable to retain anything by mouth. About 28 units of insulin were given on that day in divided doses. March 30, a large amount of sugar was found in her urine, she received an unknown amount of insulin and was sent to the hospital

The patient was stuporous but could be aroused There was an acetone odor to the breath and evidence of dehydration Respirations were of the Kussmaul type. The pulse rate was rapid, the blood pressure measured in millimeters of mercury was 108 systolic and 70 diastolic. On the palmar surface of the tip of the right fifth finger was a pustular lesion about 0 5 cm in diameter. The urine contained sugar and diacetic acid, each of grade 4 The value for blood sugar was 0 408 gm per 100 c.c, and that for the carbon dioxide combining power of the plasma 30 5 volumes per cent Regular insulin was administered and intravenous injection of physiologic saline solution was begun After this and further treatment the value for blood sugar dropped to 0 043 gm per 100 c c. and the carbon dioxide combining power of the plasma was 32 4 volumes per cent The urine contained only a trace

Sometime during the early hours of the following morning a sudden violent change for the worse took place, so that by 8 00 a m the patient presented the clinical picture of marked diabetic coma She was not completely unconscious, but could be aroused only partially and then with great difficulty The value for blood sugar was 0 526 gm per 100 c c., and the carbon dioxide combining power of the plasma had fallen to 9 3 volumes per cent With intensive treatment the status again was improved so that by 5 00 p m of the second day it was essentially the same as it had been at the same hour on the previous day, namely, the urine contained no sugar, the blood sugar was almost at a hypoglycemic level and the carbon dioxide combining power was 32 4 volumes per 100 c c. Because of the low level of the blood sugar, no further insulin was indicated then, yet the experience of the first day had taught that it would not be safe to permit the patient to go through the night without insulin She was still unable to retain anything by mouth so that it was considered inexpedient to give her regular insulin followed by carbohydrate To get around this difficulty 40 units of protamine insulin and 850 c c of a 3 per cent solution of dextrose were administered subcutaneously The level of blood sugar rose during the night to 0 380 gm per 100 c.c, and the carbon dioxide combining power fell to 24 4 volumes per cent, nevertheless, the clinical condition the following morning was improved greatly in comparison with that of the previous morning Throughout this third day ordinary insulin was used cautiously The glycosuria was controlled fairly well but the carbon dioxide

finger and metastatic abscesses necessitated amputation, the patient recovered satisfactorily from this.

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tion, depending instead, if specimens of urine are not obtainable for analysis, on frequent estimations of the value for the blood sugar. Usually catheterization is unnecessary, but when urine is not voided close watch must be kept for distention of the bladder. I have encountered cases in which relieving distention of the bladder was followed promptly by better response to treatment. The danger of a distended bladder is greatest with male patients advanced in age.

8. Dextrose.—Whether it helps to administer large amounts of dextrose in cases of acidosis is disputed. Himsworth (1932), Bertram (1932) and Rabinowitch and others (1937), have attached importance to it. Joslin, Woodyatt, Campbell and others have opposed it on the ground that the blood, and presumably the other fluids and tissues of the body, already are burdened with more sugar than can be utilized. Another objection is that when dextrose is administered intravenously, the value of the blood sugar and the tests of the urine for sugar no longer serve as guides to insulin dosage. *On the other hand, after the first two or three* hours, when the effect of what insulin has been administered is obtained, small doses of dextrose, preferably given by mouth, *serve the purpose of buffering the action of the insulin and pro*tecting the patient in case the dose chosen has been excessive.

9. Continued treatment.—When the treatment of coma is interrupted too early, the danger arises of return to a condition of coma after apparent recovery This especially is to be guarded against in the presence of infection. The following report of a case complicated by infection and illustrating "escape from control," was presented by Kepler, Ingham and Crisler to emphasize both the treacherous character of diabetic coma and the advantage which is obtained when protamine-zinc insulin is given, together with unmodified insulin It also illustrates the advantage which appears to attend the judicious use of alkali:

The patient, a white woman aged forty-two years in 1936, was found to have diabetes mellitus in 1928 Until February, 1934, the disease was controlled with small doses of insulin and a diet restricted qualitatively in carbohydrate. At that time she contracted the "flu" and diabetic coma developed After this episode she continued the former program, except that the dose of insulin had to be increased to 38 units daily. On this regimen her urine was usually sugar free.

March 24, 1936, while washing dishes, she incurred a slight puncture wound at the tip of the little finger of her right hand and the following day a small amount of pus appeared at the site of puncture March 28 she com-

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also were involved in this seasonal distribution. More than half of the patients coming to The Mayo Clinic, in the years of Adams' study, lived in rural areas and consequently led more sedentary lives in the winter than in the summer. It is probable also that their eating was not proportionately less in the winter. The suggested sequence of events was that persons susceptible to diabetes by heredity or for other reasons exercise less in winter, eat relatively too much and suffer more infections of the upper respiratory tract, and that diabetes develops in consequence not of any one, but of several of these factors.

DIABETES INTENSIFIED BY INFECTION

The absence of better evidence that infection precipitates diabetes is all the more surprising because of the demonstration by several clinicians of glycosuria, hyperglycemia and elevated blood sugar time curves in a great variety of infectious conditions in nondiabetic patients The subject has been well reviewed by Williams and Dick, who themselves found depressed tolerance for carbohydrate in 41 per cent of 108 nondiabetic patients with acute infectious diseases. Likewise, transient glycosuria was produced in animals by experimental infections. The decreased tolerance could be improved by injecting insulin, evidence that the toxemia of the infection interfered with the production of insulin, or with its action, or with both.[2] Necrosis of pancreatic tissue, including that of the islands of Langerhans, is a recognized consequence of infectious toxemias (Root and Warren), and one must presume that a pancreas which has sustained such an injury is faced with a considerable handicap When infection intervenes in the course of established diabetes of severity, the dose of insulin required may be quadrupled Does the damaged pancreas of the nondiabetic patient with scarlet fever or pneumonia rise to meet an equal demand and supply four times as much insulin as nor-

[2] Lawrence and Buckley noted inhibition of insulin activity by diphtheria toxin in rabbits It was attributable they thought to overactivity of thyroid adrenal mechanisms, but Sweeney, upon observing that injected insulin produced essentially the same effect on the blood sugar of rabbits despite a gradually rising toxemia from diphtheria toxin, concluded that the principal effect of the toxemia was to suppress the endogenous production of insulin Schwentker and Noel's studies of the carbohydrate metabolism of children with diphtheria and of rabbits

CHAPTER XI

INFECTION COMPLICATING DIABETES

DIABETES PRECIPITATED BY INFECTION

Sepsis, as Warren wrote, is the greatest foe of the poorly treated diabetic. "Just as arteriosclerosis is the bugbear of the diabetic who is doing well, so infection is the fear of the diabetic doing poorly. The more severe his diabetes the more susceptible he is to infection, and once infected his diabetes becomes far more severe." In spite of this obvious bearing of infection on pre-existent diabetes, the evidence that bacteria play a large or important part in precipitating diabetes is inconclusive. Ninety of 100 diabetic children observed by Marble had had no infection within a year of the onset of diabetic symptoms, and Lande is quoted by him as recording a similar experience from Umber's Clinic in Berlin. On the other hand, F. M. Allen's opinion, which was referred to before (see p. 44), was that acute blood-borne infection is the most common cause of subacute chronic pancreatitis and may lead to diabetes months or years later. The observations of Bertram, John, Barach and others were cited by Marble as supporting some relationship between diabetes and a preceding infectious episode.[1] Adams in our clinic analyzed 317 consecutive cases in which diabetes could be classified as acute in the sense that an abrupt appearance of symptoms served as an indication of the date of onset, and in the cases thus selected a history of preceding infection usually had been recorded; however, it frequently was too trivial to require a physician. The date of onset in these cases fell predominantly in the autumn, winter and spring, seasons when colds, acute bronchitis and the like are prevalent. However, it was pointed out that other factors

[1] In the spring of 1918, in France, an epidemic of mumps affected a company of soldiers, for whose general medical care I was responsible. There were about fifty cases in all, as I remember, and in about five of these glycosuria was associated with epigastric pain which was attributed to pancreatitis Such glycosuria in mumps usually is a transitory disturbance, but Gundersen wrote that epidemics of mumps have been followed by a rise in the death rate from diabetes in the young Jones likewise has commented on an increasing incidence of diabetes after epidemics of influenza

duced by several of the volatile anesthetics, and since loss of the activity of insulin accompanies this effect of chloroform and ether, the same probably occurs as a result of glycogen depletion by bacterial toxins. Similar loss of insulin activity is observable in most cases in which patients are recovering from attacks of diabetic acidosis The necessity for unusually large doses of insulin in these cases continues for many days after the acidosis has been fully controlled, and glycogen depletion seems to be responsible for it The fundamental difficulty in all such conditions may be cellular damage, of which a loss of ability to store glycogen constitutes only one of several evidences of abnormality. It is well known that administering dextrose or diets high in carbohydrate helps to protect the liver from the necrosis produced by chloroform and toxins; diets of this type are similarly beneficial in infections.

Finally, in many cases of infection a part is played by electrolytes. Kendall and Ingle showed that cortin administered to partially depancreatized rats provoked large excretions of potassium and water, as well as the intensification of the diabetic state previously demonstrated by Long, Fry and Thompson. No such effect on excretion of potassium was observed when normal rats were given cortin. An effect of insulin, as was shown by Harrop and Benedict, is to retard excretion of potassium, which explains why the massive doses of cortin given to their normal rats by Kendall and Ingle caused only a slight transient increase in the rate of excretion of potassium. Presumably the toxic effect of cortin is held in check by insulin, and Kendall suggested that the influence of insulin on the potassium ion may be of significance equal to its better known action on the concentration of blood sugar, that the two effects, indeed, may be inseparable. Significant in this connection is the clinical observation made by Wilbur and me, namely, that insensitivity to insulin resulting from infection, can be modified favorably by administering large doses of sodium chloride and restricting the intake of potassium

RESISTANCE TO INFECTION IN CASES OF DIABETES

Clinical experience does not indicate that the diabetic patient, when his diabetes is controlled and his nutrition is adequate, is any less resistant to infection than normal. On the other hand,

mally? Apparently it does; otherwise, intense diabetes would develop in the course of most infectious diseases, whereas Williams and Dick found mild and transient glycosuria in less than half of the infected patients in their study. Here again is an illustration of the truth of the comment made by Umber (see Chapter III), namely, that the pancreas of an individual not predisposed to diabetes possesses a capacity to meet any demand for insulin that may be created by insulin antagonists and that it even can withstand extensive damage without losing its ability to meet such increased demands.

On the other hand, the fact that the patient with pre-established diabetes requires from two to four or more times as much insulin when infection intervenes is of itself evidence of interference with the action of insulin. Just how the interference is brought about is not known; probably several factors are concerned. Rabinowitch assumed that an insulin destroying enzyme was involved. Pus cells destroy insulin in vitro; trypsin is produced by leukocytes, and the effect may be from it.[3] It was Rabinowitch's conclusion that the infection, not the fever, caused the impairment of tolerance, but other studies have demonstrated that elevating the rate of metabolism in diabetes increases the requirement for insulin (see p. 46), and it is difficult not to believe that the elevation of the basal metabolic rate that accompanies fever (DuBois) is not a factor of importance in cases in which fever is present. Also, glycogen depletion probably plays a part. That the toxins of various bacteria deplete the liver of glycogen has been shown by Fetzer. A similar depletion is pro-

[3] It was demonstrated by Bürger and Kohl that insulin when injected into an animal after clamping off the arteries to the principal masses of muscles had very [illegible] hour [illegible] no lc [illegible] this [illegible] obser [illegible] in fact, when insulin was added to blood in vitro and incubated at 37° C. (98.6° F.) for from one to [illegible] oc [illegible] bl[illegible] va [illegible] serum. The blood of patients with lymphatic or myeloid leukemia possessed a greater neutralizing effect than did the blood of patients with no leukemia, and blood of the same leukemic patients after the leukocyte count had been reduced by roentgen irradiation behaved no differently than did the blood of normal persons. The bearing of this on the relative insensitivity to insulin of diabetic patients with leukocytosis is apparent.

ing timely attention to bruises, scratches and cuts of the skin, no matter how trivial (see p. 218), are considered elsewhere If infection is local it should receive the earliest possible surgical attention; if general, energetic measures to combat acidosis are demanded. The danger of acidosis from infection often is greater if the diabetes is mild, because the patient then is likely to be unacquainted with the use of insulin and delay will occur before a suitable dose will be secured. In the presence of infection a patient usually needs insulin, even if he did not need it before. A grave mistake that patients must be taught to avoid is the omission of insulin because of nausea and their inability to eat. If the urine contains sugar and diacetic acid insulin must be administered, food or no food. It has been difficult to impress physicians sufficiently with the necessity for unusually large doses of insulin in emergencies, such as those created by complicating acute infections, operations and hyperthyroidism.

EMERGENCY INSULIN REQUIREMENT

When fever occurs with any acute disease, as well as after injuries and operations, the severity of diabetes may change from hour to hour. Therefore, in emergencies unmodified insulin must be given more frequently than otherwise is necessary and in doses which are adjusted to meet the changing tolerance A workable plan is as follows:

The urine is tested for sugar every three hours. At night the interval may be increased to six hours, but no longer period should elapse between tests Unmodified insulin is used according to the results of the tests as follows

If the grade of reaction is 4 (see frontispiece, colored plate), give 10 units of insulin Larger doses may be needed

[illegible]

with 6 units for a grade 4 reaction, 3 units for a grade 3 reaction, and 2 units for a grade 2 reaction

If the patient has been using protamine-zinc insulin and an acute illness develops which necessitates administration of more insulin, it is better not to change the dose of protamine zinc insulin but to supplement this dose with unmodified insulin to provide the extra insulin that is necessary One should give the supplementary insulin every three to six hours, according to the foregoing schedule

as the number of deaths from uncomplicated coma decreased with the advent of insulin, the relative frequency of deaths from various infections and acidosis precipitated by infection increased. Among 375 fatal cases of diabetes in Minnesota in the year 1931, Stafne found fifty-seven to be attributable to infectious complications, and in the 300 fatal cases studied by Warren acute infection was the cause of death in 126. Pneumonia was the most frequent fatal infection in Warren's series; it accounted for forty deaths. Next in importance were the pyogenic infections, causing thirty-three deaths of which five were secondary to gangrene. Focal infections of the teeth, tonsils, gallbladder and prostate gland are of importance in depressing the tolerance for sugar. They occur more frequently among malnourished, poorly treated patients.

That the nutritional state of the diabetic patient is a deciding factor in lowering his resistance to infection has been suggested by Richardson, who provoked hyperglycemia in rabbits, by injecting adrenalin, and lowered the state of nutrition by starvation. Antibody response was little affected by the former, but much more so by the latter. Moen and Reimann found, after vaccination of diabetic patients and normal controls, that agglutinins in the diabetics, when diabetes was controlled, developed in titers similar to those obtained in normal persons, but that among patients with uncontrolled diabetes the response was poor and in some cases absent. Complement was not abnormal in the cases of uncontrolled diabetes studied by Rockwood and Beeler but the opsonic index, tested with a variety of bacteria, was found to be 30 per cent lower among diabetics by Da Costa.

THE DIAGNOSIS OF INFECTION IN DIABETES

The diagnosis of infection offers some difficulty in cases of diabetes. The recognition of appendicitis is considered elsewhere (see p. 212). Acidosis is precipitated in diabetes by acute infections of many kinds, and the leukocytosis found and the pains complained of may be attributed incorrectly to it, or incorrectly to the infection.

TREATMENT OF DIABETES COMPLICATED BY INFECTION

The avoidance of infectious diseases as a means of preventing diabetic acidosis (see p. 181) and avoidance of septicemia by giv-

Soft diet—sugar value, 180 gm

Time		Grams
Breakfast	Fruit juice, 10 per cent	100
	Cereal, dry	20
	Toast	20
	Butter	10
	Cream (20 per cent butter fat)	75
	Soft cooked egg	1 egg
10 a.m	Fruit juice, 10 per cent	170
Noon	Baked potato or rice	100
	Toast	20
	Butter	10
	Cream (20 per cent butter fat)	25
	Fruit juice, 10 per cent	100
3 p.m.	Fruit juice, 10 per cent	200
Supper	Toast	20
	Butter	10
	Soft cooked egg	1 egg
	Fruit (10 per cent)	100
8 p m	Fruit juice, 10 per cent	200
This diet contains approximately		Grams
	Carbohydrate	160
	Protein	24
	Fat	59
	Calories	1267

TUBERCULOSIS COMPLICATING DIABETES

Excellent reviews of this subject have been written by Root (1934) and by Himsworth. The incidence of association of pulmonary tuberculosis and diabetes is much less than in former days, when Naunyn found pulmonary tuberculosis in 41 per cent of necropsies on diabetic patients, nevertheless, it still is high. Pulmonary tuberculosis was the cause of 5 2 per cent of the deaths of the diabetic patients of the George F. Baker Clinic between August 7, 1922 and March 13, 1935, and in the same institution among 1121 necropsies on diabetic patients active tuberculosis was discovered in 28.4 per cent. Himsworth, carefully examining the patients in 230 consecutive cases of diabetes, found fifteen (6 5 per cent) with tuberculous lesions of the lungs Root, in 1126 cases in which diabetes developed before the patients were fifteen years of age, subsequently found seventeen cases of tuberculosis and compared this incidence of 1.5 per cent with that for tuberculosis in the school population of Massachusetts, which Pope in 1934 estimated to be 0.12 per cent. In cases in which adults who had diabetes were examined by roentgenograms of the thorax at the George F. Baker Clinic, tuberculosis was discovered

When the emergency has passed and convalescence begins, the tole may rise rather quickly, and reactions will be encountered unless the of insulin are diminished. Safety is assured by testing the urine not less quently than four times a day and decreasing the doses as the results of tests improve When recovery is complete, the maintenance diet may resumed, usually the dose of insulin that was effective before the emergen will again suffice

EMERGENCY DIETS

A complicating illness of any kind frequently makes it necessary to alter the diet by restricting the total amount of nourishment and omitting foods which are digested less readily. The diets shown are designed for this pur pose The liquid diets are for patients who are very sick or recently have undergone operations The soft diet is intended for less serious conditions These diets provide from 120 to 180 gm. of carbohydrate, an amount which such patients ought always to receive. If the food is not eaten, or if it is vomited, 150 gm of dextrose should be injected into the rectum in the course of the day, or given by vein For the rectal injection the dextrose may be dissolved in 2 quarts of tap water, and 1 pint of the solution, warmed t body temperature, given every six hours The "Murphy drip" method i recommended For intravenous administration nothing but the purest dex trose will do It should be made into a 10 per cent solution with triple distilled water and sterilized before injection

Orange juice diet—sugar value, 130 gm.

Time		Grams		Grams	Total carbo hydrate, grams
a m					
8	Orange .	150	Sugar	5	20
10	Orange juice	150			15
12 noon	Orange juice	150	Sugar	5	20
p m					
2	Orange juice	150			15
4	Orange juice	150	Sugar	5	20
6	Orange juice	150			15
8	Orange juice	150.	Sugar	10	25

Milk diet—sugar value, 120 gm.

Time		Grams
a m.		
8	Skimmed milk	250
10	Skimmed milk	250
12 noon	Skimmed milk	250
p.m		
2	Skimmed milk	250
4	Skimmed milk	250
6	Skimmed milk	250
8	Skimmed milk	250
	Skimmed milk	250

Soft diet—sugar value, 180 gm

Time		Grams
Breakfast	Fruit juice, 10 per cent	100
	Cereal, dry	20
	Toast	20
	Butter	10
	Cream (20 per cent butter fat)	75
	Soft cooked egg	1 egg
10 a.m	Fruit juice, 10 per cent	170
Noon	Baked potato or rice	100
	Toast	20
	Butter	10
	Cream (20 per cent butter fat)	25
	Fruit juice, 10 per cent	100
3 p.m	Fruit juice, 10 per cent	200
Supper	Toast	20
	Butter	10
	Soft cooked egg	1 egg
	Fruit (10 per cent)	100
8 p.m	Fruit juice, 10 per cent	200
This diet contains approximately		Grams
	Carbohydrate	160
	Protein	24
	Fat	59
	Calories	1267

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When the emergency has passed and convalescence begins, the tolerance may rise rather quickly, and reactions will be encountered unless the doses of insulin are diminished. Safety is assured by testing the urine not less frequently than four times a day and decreasing the doses as the results of the tests improve. When recovery is complete, the maintenance diet may be resumed, usually the dose of insulin that was effective before the emergency will again suffice

EMERGENCY DIETS

A complicating illness of any kind frequently makes it necessary to alter the diet by restricting the total amount of nourishment and omitting foods which are digested less readily. The diets shown are designed for this purpose The liquid diets are for patients who are very sick or recently have undergone operations The soft diet is intended for less serious conditions These diets provide from 120 to 180 gm of carbohydrate, an amount which such patients ought always to receive. If the food is not eaten, or if it is vomited 150 gm of dextrose should be injected into the rectum in the course of the day or given by vein. For the rectal injection the dextrose may be dissolved in 2 quarts of tap water, and 1 pint of the solution, warmed to body temperature, given every six hours. The "Murphy drip" method is recommended For intravenous administration nothing but the purest dextrose will do It should be made into a 10 per cent solution with triple distilled water and sterilized before injection

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Time a m		Grams		Grams	Total carbohydrate, grams
8	Orange	150	Sugar	5	20
10	Orange juice	150			15
12 noon	Orange juice	150	Sugar	5	20
p m.					
2	Orange juice	150			15
4	Orange juice	150	Sugar	5	20
6	Orange juice	150			15
8	Orange juice	150	Sugar	10	25

Milk diet—sugar value, 120 gm

Time a m.		Grams
8	Skimmed milk	250
10	Skimmed milk	250
12 noon	Skimmed milk	250
p m	Skimmed milk	250
2	Skimmed milk	250
4	Skimmed milk	250
6	Skimmed milk	250
8	Skimmed milk	250

Soft diet—sugar value, 180 gm

Time		Grams
Breakfast	Fruit juice, 10 per cent	100
	Cereal, dry	20
	Toast	20
	Butter	10
	Cream (20 per cent butter fat)	75
	Soft cooked egg	1 egg
10 a.m.	Fruit juice, 10 per cent	170
Noon	Baked potato or rice	100
	Toast	20
	Butter	10
	Cream (20 per cent butter fat)	25
	Fruit juice, 10 per cent	100
3 p.m.	Fruit juice, 10 per cent	200
Supper	Toast	20
	Butter	10
	Soft cooked egg	1 egg
	Fruit (10 per cent)	100
8 p.m.	Fruit juice, 10 per cent	200
This diet contains approximately:		Grams
	Carbohydrate	160
	Protein	24
	Fat	59
	Calories	1267

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4	Orange juice	150	Sugar	5	20
6	Orange juice	150			15
8	Orange juice	150	Sugar	10	25

Milk diet—sugar value, 120 gm

Time a m		Grams
8	Skimmed milk	250
10	Skimmed milk	250
12 noon	Skimmed milk	250
p m	Skimmed milk	250
2	Skimmed milk	250
4	Skimmed milk	250
6	Skimmed milk	250
8	Skimmed milk	250

Soft diet—sugar value, 180 gm

Time		Grams
Breakfast	Fruit juice, 10 per cent	100
	Cereal, dry	20
	Toast	20
	Butter	10
	Cream (20 per cent butter fat)	75
	Soft cooked egg	1 egg
10 a.m	Fruit juice, 10 per cent	170
Noon	Baked potato or rice	100
	Toast	20
	Butter	10
	Cream (20 per cent butter fat)	25
	Fruit juice, 10 per cent	100
3 p m.	Fruit juice, 10 per cent	200
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in 2.8 per cent. These patients were not bed patients but had been admitted for dietary treatment and instruction. The observation, therefore, may be compared with community surveys and examinations for draft boards, in which the usual incidence of tuberculosis is 1 per cent.

Possibly because the proportion of young persons coming to The Mayo Clinic is relatively small, the incidence of tuberculosis among our patients has been comparatively low. Roentgenograms of the thorax have been obtained in at least three of every four cases in which the diagnosis of diabetes mellitus has been established, yet for the years 1935 to 1937, inclusive, among 2584 diabetic patients examined the diagnosis of active pulmonary tuberculosis was established in only fourteen (0.54 per cent). For comparison, the incidence of pulmonary tuberculosis among all new patients coming to The Mayo Clinic in 1937 was 0.78 per cent, but the average age of the diabetic patients was 52.8 years, whereas that for all new patients in 1937 was 41.6 years.[4]

Both Himsworth and Root (1934 and 1937) have emphasized that early pulmonary tuberculosis among diabetic patients is difficult to recognize, and that roentgenologic examination of the thorax is necessary in all cases and ideally should be obtained every year. The early lesions tend to be deep-seated and those situated further out in the lung tend to spread more rapidly toward the hilum than to the periphery of the lung. The type of lesion usually is pneumonic with little fibrosis and inconspicuous physical signs. Pleuritis and adhesion of the lung to the wall of the thorax are uncommon. Himsworth commented that the pneumonic type of lesion spreading to the hilum has been noted so frequently in diabetes that Sosman and Steidl considered it a characteristic of diabetes, "diabetic tuberculosis." This type of lesion was found in twenty-one of their twenty-nine cases.

The effect of tuberculosis on diabetes varies. It is likely to be unfavorable if secondary infection occurs. On the other hand, with rapidly advancing tuberculosis associated with much cachexia, sensitivity to insulin may increase so that a small dose will

[4] Prevalence of pulmonary tuberculosis in European cities is much greater in general than that encountered in America, and in Paris, among patients with diabetes, Roy found that it was 16.5 per cent! The disease was much more frequent among uncontrolled [illegible] The course of the combined disease was very unfavorable, rarely [illegible] years in duration, with tuberculosis the cause of dea[illegible] 7 per

provoke reactions. The fact that tolerance for carbohydrate by diabetic patients increased if the patients became cachectic from tuberculosis or other causes prompted F. M. Allen to undertake his classical investigation of the effect of starvation in diabetes.

The outlook for patients with diabetes complicated by tuberculosis is by no means as hopeless as has been supposed. Although the evidence clearly indicates that lack of control of the metabolic condition of the patient predisposes to the development and extension of tuberculous lesions of the lungs, it also shows that good therapeutic results are possible if good management is obtainable. Unfortunately the staff physicians of many hospitals for tuberculosis patients have not been prepared to treat diabetes. Excellent results have been obtained by Callahan in the Pokegama Sanatorium with patients we have referred to him. Also Myers and McKean, in a series of eighty cases of diabetes, obtained arrest, or apparent arrest, of pulmonary tuberculosis in 21 per cent of the cases in which it was moderately advanced (class 2), in 25 per cent of those in which it was more advanced (class 3B), and in 10 per cent of those in which it was advanced (class 3C). Eventual arrest was anticipated in an additional 43 per cent of the cases in class 2 and in another 16 per cent of those in class 3B. The results compared favorably with those for nondiabetic patients with tuberculosis of less severity in the same hospital. The average amount of insulin needed to bring the diabetes under control was 46 units daily. The average dose at the time of dismissal was 42 units daily. The average diet contained 108 gm. of carbohydrate, 62 gm of protein and 162 gm. of fat. In its relatively low content of protein and its relatively high fat-carbohydrate ratio it was similar to that which McCann and Barr found best adapted in cases of uncomplicated pulmonary tuberculosis.

The use of insulin to the point of hypoglycemia to improve tuberculosis is not recommended. The extensive literature on the subject was reviewed by Allen (1936). The value of artificial pneumothorax and phrenectomy in the treatment of the tuberculosis of diabetic patients also has been emphasized by Myers and McKean.

"In some way the resistance to tuberculosis is lowered during emaciation" (Root, 1937). It is for this reason that I deplore the survival of the theory of undernutrition in present day man-

Allen, F. M: Insulin and tuberculosis; a partial review of the literature and bibliography. Am Rev. Tuberc, 34: 230–256 (Aug) 1936

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Naunyn, B Quoted by Himsworth, H P

von Noorden, C and Isaac, S: Die Zuckerkrankheit und ihre Behandlung Ed 8, Berlin, Julius Springer, 1927, p 291

agement of patients who have diabetes mellitus. If diabetes predisposes to tuberculosis, it seems to me to be essential to keep these patients not 10 per cent or more under the average weight for persons of their height and age, but, if possible, at average weight. On similar grounds a good case can also be made for not rigidly restricting the proportion of fats in diabetic diets. Low values for blood lipoids are commonly found in patients with tuberculosis, and the highest death rates from tuberculosis, as is well known, are encountered today in the tropics among persons whose diets are notoriously high in carbohydrate and lacking in animal fats (Wilder, 1935). Prevention of tuberculosis can never effectively be accomplished without preliminary attention to the adequacy of nutrition.

OTHER PULMONARY INFECTIONS; PNEUMONIA

The low resistance of diabetic patients may not apply to other infections of the lungs. At the New England Deaconess Hospital the clinical diagnosis of pneumonia was made in only seventy-three (0.5 per cent) of 13,188 cases of diabetes. Likewise Delijannis found both lobular and lobar pneumonia to be conspicuously less frequent in necropsies on diabetic patients than in other necropsies. The diagnosis of pneumonia, as Marble has written, must often be faulty in cases of diabetes; coma is often blamed for deaths which pneumonia has caused, and the reverse also occurs. Pain in the thorax at the beginning of coma may be due either to acidosis or to associated pneumonia.

Pulmonary abscess and gangrene, other than what may result from secondary infection in tuberculosis, have not been encountered among the cases of diabetes that have come to my attention. In the text of von Noorden and Isaac is the statement that pulmonary gangrene is seen on occasion in diabetic patients following lobar pneumonia, bronchopneumonia, traumatic injuries of the thorax and bronchitis, and that apparently on rare occasions it may develop spontaneously.

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OTHER PULMONARY INFECTIONS; PNEUMONIA

The low resistance of diabetic patients may not apply to other infections of the lungs. At the New England Deaconess Hospital the clinical diagnosis of pneumonia was made in only seventy three (0.5 per cent) of 13,188 cases of diabetes. Likewise Delijannis found both lobular and lobar pneumonia to be conspicuously less frequent in necropsies on diabetic patients than in other necropsies. The diagnosis of pneumonia, as Marble has written, must often be faulty in cases of diabetes; coma is often blamed for deaths which pneumonia has caused, and the reverse also occurs. Pain in the thorax at the beginning of coma may be due either to acidosis or to associated pneumonia.

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CHAPTER XII

SURGICAL OPERATIONS IN DIABETES[1]

In the era before insulin, as Joslin has said, "there were few diabetic patients and their life was short and firmly bound with chains of acidosis and undernutrition. Today there are many diabetics because they live longer and insulin has set them free." He estimated that every third person who had diabetes and probably "every other diabetic at some time during the course of his disease needs the surgeon and will seek him not in vain, provided he secures the co-operation of accurate and interested technicians, faithful nurses, and doctors conversant with diabetes."

Operating on patients with this disease formerly involved a hazard which few surgeons were willing to accept. The rates of mortality encountered varied from 18 to 46 per cent, and although this was due in some degree to operating mostly for emergencies, as a measure of last resort, it was largely attributable to the lack of effective means for preventing the development of acidosis The hazard in these cases is still serious, but may be overcome by employing skillful surgery, the best possible anesthesia and modern methods of controlling acidosis Trauma to tissue, shock from loss of blood and prolonged anesthesia are poorly borne in diabetes and neglect of these patients before and after operation often leads to dangerous acidosis. The attendance of physicians and nurses who possess special experience in diabetes is desirable, and closest co-operation between surgeon and physician is imperative. Every case in which operation must be performed in the presence of diabetes is a potential case of coma and should be treated accordingly. The statement applies whether the diabetes is severe or mild, and whether the operation contemplated is major or minor. Mild diabetes may be made severe by anesthesia and operative trauma, and the tendency of some surgeons to belittle the significance of a trace of sugar has led to fatalities.

[1] This chapter, with some alterations, is reprinted from an article by Walters, Meyerding, Judd and Wilder, and with many of these alterations, was presented by Walters and Kepler before the Summer School of the Vancouver Medical Association, Vancouver, British Columbia, Canada, June 21–24, 1938

The importance of preoperative attention to the diabetes of diabetic patients requiring surgery has been emphasized by Standard, Brandaleone and Ralli, writing from the Third (New York University) Surgical and Medical Divisions of the Bellevue Hospital. In a group of 474 surgical diabetic patients, 172 were treated preoperatively in the diabetic clinic of the medical service The mortality for the patients treated in the clinic was 6 9 per cent, while in the group not so treated it was 20.8 per cent. The lower mortality in the group treated in the clinic was noticeable following all surgical procedures, but was most striking in the cases requiring major amputations.

SURGICAL RISK

From 1921 to 1932, inclusive, 1,028 major and 1,058 minor surgical procedures were performed on diabetic patients at The Mayo Clinic.[2] The selection of patients for operation was made on the same indications as those obtaining for nondiabetic patients, and no patient was declined for operation on the basis of diabetes of greater or lesser severity. The deaths numbered sixty-nine, a mortality rate, based on number of operations, of 3.3 per cent. In later years the mortality rate increased to 4.5 per cent in 1935, to 5.1 per cent in 1936, 7.5 per cent in 1937, and 6 2 per cent in 1938. The reasons were a greater proportion of operations for carcinoma of the stomach and large intestine and the advancing age of the patients as their life span was lengthened by insulin. The increase has not resulted from inability to con-

[2] The classification of the operations of this and later series into major and minor groups has been as follows: Multiple procedures on separate dates are counted as separate operations, multiple procedures on the same date are counted as one operation and listed under the principal procedure The major operations include. the procedures in which a body cavity (pleura, peritoneum, joint, eye-

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counted as one minor operation

Re-application of casts, removal of drainage tubes, removal of sutures, other surgical dressings, and intravenous injection of fluids other than blood and drugs are not counted as operations

preoperative and postoperative care, the younger patient with severe diabetes tolerates surgical procedures with little additional risk because of his diabetes.

DIAGNOSIS OF SURGICAL LESIONS OF ABDOMEN IN PRESENCE OF DIABETES

The diagnosis of acute abdominal lesions, especially appendicitis, presents some difficulty when the patient has diabetes. This is because many of the signs and symptoms of diabetic acidosis are in many respects the same as, or like, those resulting from lesions requiring surgery. Thus, nausea and vomiting, abdominal pain and tenderness, rapid pulse, and leukocytosis, all are symptoms of diabetic acidosis and of themselves are not indicative of abdominal disease. We once encountered a case of pure diabetic coma in which the leukocytes in the blood exceeded 60,000 per cubic millimeter, and counts of from 15,000 to 20,000 are not at all uncommon. Fever, if present, is attributable to some infection, but this may be in the respiratory tract and not in the abdomen. On the other hand, an acute inflammatory lesion in the abdomen may underlie and be responsible for the existing acidosis.

A careful history should be taken in these cases. Abdominal *pain preceding the onset of the other symptoms speaks for* a surgical emergency, particularly if the onset of the pain is acute, whereas a gradual onset with polyuria and polydipsia preceding the abdominal pain probably means acidosis One is guided also by the presence or absence of localized rigidity of the abdominal wall and by localized tenderness. The rigidity encountered in diabetic acidosis is diffuse, as is the tenderness. If doubt remains, an operation usually should be performed.

TIMING THE OPERATION

In the presence of surgical emergencies nothing is to be gained by delaying operation; indeed, when a curable infection exists, delay may be harmful. This applies especially to amputations of extremities for rapidly spreading gangrene with infection and to acute appendicitis, pelvic abscesses, mastoiditis and other inflammatory processes. In such conditions the infection is the primary consideration, and the operation should not be delayed even to

control intense glycosuria and acidosis. Such a patient at The Mayo Clinic is given 1000 c c of physiologic salt solution intravenously and a preliminary dose of insulin (the exact amount depends on the severity of the diabetes, the age of the patient and other factors). The operation is then performed without further delay. On the other hand, when a surgical lesion is not infected, or when an existing infection is chronic and has little or no influence on metabolism, there is not such excuse for haste, and time should be taken to secure the most favorable conditions before operating. The aims are complete freedom from acidosis, a sugar-free or nearly sugar-free urine, and adequate reserves of glycogen, fluids and salts.

ATTENTION BEFORE OPERATION

The routine preoperative procedure at The Mayo Clinic has been as follows The patient is observed in the hospital for two or more days while a measured diet is prescribed and sufficient insulin is used to clear the urine of sugar and to free it of ketone bodies The diet for these patients is made liberal enough in carbohydrate to provide adequate dextrose for storage as glycogen but we have not found it necessary or desirable, except in operations on the biliary tract and in cases of hyperthyroidism, to resort to high allowances of carbohydrate such as have been recommended in some other clinics. Our preoperative diets usually have contained about 200 gm. of carbohydrate. If dehydration is apparent, fluids are given by rectum or by vein In cases of mild diabetes, on the morning of operation, both breakfast and insulin are withheld. Patients with very severe diabetes under control with regular insulin are given a half to two-thirds of the usual dose of insulin even though breakfast is withheld Patients who are taking protamine-zinc insulin are given a half to two-thirds of the usual dose of the protamine preparation but supplementary regular insulin is usually not given immediately prior to the operation. The intravenous injection of solutions of dextrose is valuable as a preoperative and postoperative measure in cases of jaundice and in other cases in which there is reason to suspect some degree of hepatic insufficiency. Insulin is added to the solution in the amount of 1 unit for each 5 gm of the sugar.

In the preoperative and postoperative treatment of diabetic

patients who have surgical complications and in the treatment of diabetic acidosis, protamine-zinc insulin has proved to be of value. Situations not infrequently arise in which, although the preoperative use of short-acting insulin will be contraindicated, the status of the patient will be such that several hours later insulin will be needed. Protamine-zinc insulin can be given with comparative safety prior to the operation, for by the time its peak effect is reached the operation is over. The daily use of protamine-zinc insulin, supplemented as necessary with regular insulin, is continued throughout the postoperative period until the patient is back on his usual diet and doses of insulin. When this program is followed, there is very little danger that the disease will get out of hand during the immediate postoperative period, although, following tonsillectomy in two of our cases of severe diabetes in which treatment included the foregoing preoperative and postoperative program, severe acidosis and incipient coma developed and necessitated the use of large doses of unmodified insulin.

THE ANESTHESIA

The choice of anesthetic depends on the surgical indications General anesthetics are poorly borne in diabetes They may produce some degree of hyperglycemia and acidosis in normal persons, and postoperative vomiting and unavoidable starvation intensify this condition Anesthetic methods and agents in the order of preference are: (1) local, regional and spinal anesthesia, (2) ethylene, cyclopropane, nitrous oxide, and the intravenous anesthetics (pentothal sodium), and (3) ether. However, when ether can be expected to provide better relaxation and therefore to expedite and shorten time of operation or reduce the degree of surgical trauma, it may be preferred. In some clinics an intravenous injection of insulin and dextrose is given during the course of operation We have not found this necessary or desirable The most important single factor is that the surgical procedure should be carried to completion with accuracy and celerity. A minimum of trauma and a minimum of anesthetic time are crucial.

ATTENTION AFTER OPERATION

As soon as the patient has returned to his bed, he is treated with insulin and injections of fluid. Saline solutions are preferred

to solutions of dextrose, because dextrose, given parenterally, escapes the glycogen barrier of the liver and is in part excreted in the urine, even in individuals who are adequately supplied with insulin. This vitiates urinalysis as the gauge to the amount of insulin needed[3] Sugar is usually in high concentration in the blood after operation, and for a time at least it seems unnecessary to provide additional sugar The dose of insulin must be judged at first from periodic determinations of the concentration of blood sugar. Later, when excretion of urine begins, each specimen of urine, as it is voided, is immediately analyzed for sugar, and these analyses, as has been described under "Emergency insulin requirements" (p 201), enable a reasonably accurate appraisal of the demand for insulin It must be remembered that the time of action of regular insulin is shortened by anesthesia, infection and trauma, and that the intervals between injections must be shortened One injection every six hours is required, but no absolute rule about this is safe. The dose must be determined largely by previous experience with the particular patient and by frequent analyses of the blood and urine for sugar.

The danger of overdosing with insulin should be constantly in mind. We attribute one of our fatalities to insulin shock. The patient went into shock four hours after operation and, although he was restored to consciousness, fatal bronchopneumonia developed It may have been precipitated by the period of apnea that accompanied the severe insulin reaction. The physician in charge of these patients must be trained to recognize quickly any evidence of metabolic abnormality. Acidosis threatens on the one hand, hypoglycemia from overuse of insulin on the other. It is probably safer to err on the side of too little control than too much, at least for the first day or two after operation, and until the patient can begin to co-operate effectively. Slight glycosuria will do little harm; an attack of insulin coma has much more serious consequences.

Diets for surgical patients.—Diets after operations must be adjusted to meet various special indications. In other words, the treatment of the diabetes of surgical patients is to be subordinated

[3] When circumstances arise in cases of diabetes which make intravenous injection of dextrose desirable, we have found it satisfactory to add unmodified insulin to the solution for injection in amounts representing one unit for each 5 gm of dextrose

to the treatment of the patient. This can usually be effected without difficulty by examining the urine three or four times daily, testing the blood at intervals and adjusting the doses of insulin to the changing requirements. When not otherwise objectionable we like to start oral feedings after the first twenty-four hours, giving at first only fruit juice, ginger ale, or a 10 per cent solution of dextrose, then milk, cereals, custards and other bland foods, and gradually other foods until a satisfactory maintenance regimen has been established

It is important in most cases to keep the patient under very close supervision, if not actually in the hospital, until the diet he is expected to follow at home has been demonstrated, and he has been taught what he needs to know to control his diabetes at home.

HEALING OF WOUNDS

The healing of surgical incisions is delayed when treatment of diabetes is inadequate—not otherwise. Bennett, a former fellow in The Mayo Foundation, studied surgical wounds in dogs which had been made diabetic by pancreatectomy. The pancreas was removed under ether anesthesia. The animals were supported with insulin and a suitable regimen until they had recovered completely. Then insulin was withheld, and when the ensuing diabetic state had developed, abdominal incisions were made under local anesthesia. As compared to the behavior in identical wounds in healthy animals used as controls, the healing of these wounds was abnormal. The tissues were edematous, deposit of fibrin was delayed and the amount of fibrin was restricted. The cellular reaction was excessive and the exuded cells appeared to be of the so-called toxic type. New blood vessels were slow to form, and more thrombosis than normal was noted in pre-formed vessels. On the other hand, healing proceeded perfectly normally when the diabetes was well controlled.

The presence of an excess of sugar in tissues was formerly thought to favor infection but probably is harmless, provided insulin is acting and the metabolism of the cells is undisturbed In two cases of clean abdominal wounds, I deliberately gave only enough insulin to control acidosis, and in these cases the wounds closed in normal time by primary intention, even though the

range of the blood sugar in one case was as high as 0.4 gm per 100 c.c.[4] On the other hand, when the supply of blood is impeded, as in the stump left after amputation of an extremity for occlusive vascular disease and gangrene, the presence of sugar in the tissues may predispose to infection and thus interfere with healing.

SURGICAL TREATMENT OF GANGRENE

The old rule either to operate early and operate high or treat the lesion medically and avoid all surgical treatment has guided us to a mortality rate in diabetic gangrene that is comparatively very low. When we deviate from it, we usually regret doing so. Primary amputation through the foot for removal of gangrenous toes was performed in fifteen such cases, reviewed by Allan and Kintner, and higher amputation became necessary in a third of them. The ultimate outcome was fatal in 20 per cent. By contrast, in seventy-one cases of gangrene of the toes or foot, in which primary amputation was through the leg, a secondary operation was required in only four, and the mortality was only 7 per cent The cases chosen for amputation of toes, reviewed by Allan and Kintner, were suitable by all ordinary criteria, the gangrene was limited to the toes, pulsation of the dorsalis pedis and posterior tibial arteries was fair, the extremity was not cold, and there was no great difference in blanching or reddening on elevating or lowering the leg. Yet the mortality rate in this group almos equaled that observed in an additional sixty-seven cases in whic medical treatment alone was provided. Once amputation is d cided on, it should be done below the knee, provided pulsati is good in the popliteal artery; above the knee if the pulsation this artery is inadequate. A well-fitting artificial leg, or eve wooden peg, is to be considered an asset in the light of the dar of imperfect healing of wounds after amputation of toes diabetic gangrene.

These observations do not apply to perforating ulcers, c sores, and other chronic infections of the feet which are n companied by massive necrosis of tissue or gross impairme

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These observations do not apply to perforating ulcers, other sores, and other chronic infections of the feet which are not accompanied by massive necrosis of tissue or gross impairment of

[4] Bayne Jones has expressed the opinion that the concentration of sugar in the blood has little or nothing to do with susceptibility to infection in diabetes, since blood in vitro to which enough dextrose has been added so that it contains from 0 1 to 0 5 per cent dextrose is no more suitable as a culture medium for staphylococci than blood without added sugar.

circulation. In such cases the leg usually can be saved by medical measures, but if cellulitis develops in a case in which there is much arteriosclerosis, and if it is clearly advancing and reaches the ankle, high amputation is desirable and should be done without delay.

TREATMENT OF ULCERS AND OTHER SORES

Lesions of the feet that are not accompanied by gross occlusion of the circulation usually are precipitated by infection. They include infected corns and calluses, perforating ulcers, osteomyelitis, burns, frost-bite, varicose ulcers and septic abrasions. Osteomyelitis of a phalanx should be suspected in every localized infection of more than two weeks' duration in any part of a toe or foot (McKittrick and Root). The diagnosis is made roentgenologically or by encountering rough bone with the probe. The perforating ulcer, and indeed many of the indolent, infectious conditions of the feet in diabetes, may in part be dependent on the presence of peripheral neuritis. The feet in such cases are abnormally insensitive, and complaints of numbness and of aching pains at night are common. Much needless suffering results from unnecessary delay in the treatment of infections of the feet. Diabetic patients should learn to treat all abrasions seriously, and immediately to apply a nonirritating antiseptic, such as the mixture of boric acid and alcohol. Prophylactic measures also are important, especially clean socks and well-fitting shoes (see p 340).

The medical care of ulcerated or infected extremities, with or without gangrene, is to enforce absolute rest in bed with the foot very slightly elevated above the horizontal plane, and rigidly to control glycosuria.[5] If the gangrene is dry and not grossly infected, a dry dressing is best, but if infection is present, the old Ochsner dressings of gauze and cotton are recommended. These are made 1 inch (2.5 cm.) thick and kept saturated with a mixture of equal parts of 50 per cent alcohol and saturated solution of boric acid. They should be large enough not only to cover the lesion, but also a large part of adjacent skin. If the lesion

[5] A high renal threshold for dextrose develops in many cases of diabetes of long duration, and under these circumstances the tissues may require a concentration of blood sugar that is higher than normal. Consequently, it is not desirable to force the concentration of blood sugar lower than is necessary to avoid glycosuria

is on the foot, the entire foot and the lower third of the leg should be covered. The infection either starts to subside within twenty-four hours after applying the measures enumerated, or by this time gives clear evidence of advancing. If it subsides, the treatment is continued until the infection is fully controlled, and then the decision is made whether the degree of accompanying gangrene or the degree of circulatory impairment justifies amputation. If it fails to subside, after twenty-four hours of treatment with alcohol and boric acid, amputation is usually recommended. If the redness and swelling extend beyond the ankle, immediate amputation is urged. The possibility of a superimposed infection with gas-producing organisms should always be kept in mind and treatment with suitable antitoxin instituted if there is the slightest doubt regarding its presence. In the presence of infection with gas-producing organisms treatment with roentgen rays also is beneficial. Maes has called attention to the frequency with which bandages and blankets of wool are infected with the spores of gas bacilli. By avoiding the use of wool wrappings for the legs of patients with gangrene before and after operation, he materially diminished the occurrence of this complication.

In some cases it may be possible to improve the peripheral blood flow by vasodilating drugs and thereby to hasten healing Among such drugs, theobromine in doses of 10 to 15 grains (0.65 to 1 gm.) three or four times daily is sometimes effective, as is also alcohol. An ounce of alcohol, prepared as a highball is given two or three times a day. Horton found alcohol to be more effective if the room temperature is between 80° and 83° F. Pancreatic tissue extract is not a vasodilating agent but has been found helpful in the treatment of intermittent claudication. Barker, Brown and Roth recommended a dose of from 1 to 3 c.c. daily, injected subcutaneously The treatment of circulatory impairment includes the use of therapeutic measures such as the daily massage, contrast baths and postural exercises used in thrombo-angiitis obliterans (Buerger's disease). On the whole, the results of treatment with the pavex or intermittent suction and pressure machine have not been up to expectation. An occasional patient may be benefited; some have been made worse.

It is important always to remember that the skin of diabetic patients with arteriosclerosis will burn and blister at temperatures

well below those which would not be injurious otherwise, and that any application of heat demands exercise of extreme caution The same caution is important in applying roentgen treatment to extremities of diabetic patients. We have seen two cases of diabetes in which necrosis of tissue followed treatment elsewhere with doses of roentgen rays that were of average therapeutic magnitude. Exposures to sunlight or ultraviolet light also are beneficial, but caution to avoid burning is again necessary. A general rule that seems to have helped in our hospitals is that no hot water bags or other applications of heat are to be made below the knees of diabetic patients without the written order of the physician or surgeon who is responsible.

TREATMENT OF CARBUNCLES

Carbuncle is a deadly complication in diabetes. The mortality rate is reported to be from 25 to 60 per cent. Fortunately carbuncle occurs infrequently and is nearly always preventable by cleanliness and proper attention to the control of glycosuria. We had only twenty-six cases of carbuncle in a period of sixteen years, and not more than twice this number of cases of furunculosis. The patients for the most part were obese and uncleanly, and had paid little or no attention to the treatment of their diabetes.

The most important measure for the prevention of carbuncle is the admonition of Price on the subject of pimples and boils: "Don't squeeze, don't prick, don't cut." To this McKittrick and Root properly added: "Don't show sugar, and do respect an infection no matter how small it may be." A further wise admonition is to avoid the customary shaving of the neck at the barber shop. Boils are frequently due to infection from barbers' razors, and carbuncles may *follow boils. It is wise for the diabetic patient to use his own razor*

Leddy and Morton have reported that roentgen rays may hasten localization in cases of carbuncle and may lessen pain. The wide crucial incision of a carbuncle, extending throughout the zone of induration, seems a particularly bad form of treatment. It must lead to extension of infection and septicemia in many cases.

At present in cases of carbuncle with diabetes, operation is

avoided entirely at The Mayo Clinic. The essential items in the treatment are: (1) absolute rest in bed, (2) rigid control of glycosuria, (3) thick gauze and cotton dressings saturated with equal parts of boric acid and 50 per cent alcohol, kept warm (not hot) and (4) daily intravenous injection of 10 c.c. of 40 per cent solution of methenamine for a week. After central necrosis of the carbuncle has occurred and natural drainage has established itself, but not until then, a pair of sterile artery forceps is introduced and gently opened to hasten drainage Occasionally the destruction of skin necessitates skin grafting, but this is not the rule

A discussion of the rationale of treatment with methenamine has been given by von Takáts The dose used is large enough so that traces of formaldehyde have been demonstrated in pus taken from the center of the carbuncle. The growth of bacteria is probably inhibited by this trace of formaldehyde, and possibly also the natural defenses of the organism are stimulated by the drug.

The value of sulfanilamide and related compounds in the treatment of carbuncle, in which the infecting organism usually is the staphylococcus, at present is under consideration. In the few cases of diabetes in which these drugs have been used, no unusual toxicity has been encountered.

DEXTROSE AND INSULIN IN NONDIABETIC SURGICAL CASES*

RANDALL G SPRAGUE, M D

There is much of theoretic interest and practical importance in the clinical study of the metabolism of dextrose by nondiabetic individuals who are undergoing surgical procedures. The internist frequently is confronted with the question of the interpretation of glycosuria occurring after infusion of dextrose in treatment of surgical patients. The surgeon is interested in questions of the value of insulin and of dextrose in the treatment of certain postoperative complications, such as shock, acidosis and poor healing of wounds Aid in answering these questions is found in an analysis of certain known facts concerning the tolerance of the organism for dextrose and the action of insulin in the nondiabetic organism.

According to data obtained from experiments on dogs and

*Editorial prepared for Minnesota Medicine (22 619–650 [Sept] 1939), reprinted with permission

normal men, the individual having a normal ability to store and oxidize carbohydrate can receive dextrose by the intravenous route at the rate of about 0.85 gm. per kilogram of body weight per hour without excreting abnormal amounts in the urine. Thus, a normal man weighing 70 kg. should have no glycosuria if a liter of 10 per cent solution of dextrose was infused at a uniform rate during approximately two hours. The postoperative surgical patient, however, may exhibit for a variable period a diminished ability to utilize dextrose, for at least two reasons: (1) starvation, and (2) the surgical procedure itself, including the anesthesia. Obviously, there is no easy way of estimating the extent of this diminution in tolerance in any given case. Hence, the interpretation of glycosuria after infusion of glucose may be difficult and further investigation may be necessary before previously unsuspected diabetes can be definitely excluded. This investigation should consist, first, of determination of blood sugar after a night's fast. In cases in which doubt still remains, a dextrose tolerance test may be necessary. The patient on whom such a test is made should have fully recovered from the operation and, for several days before the test, he should have been supplied with liberal amounts of carbohydrate food. In the routine management of patients after operation, however, it is possible to avoid raising a suspicion of diabetes unnecessarily if dextrose is infused at a rate well under the normal limit of utilization; that is, if a man is of average body weight it is well to take three to four hours for the infusion of a solution containing 100 gm. of dextrose. If glycosuria occurs repeatedly with such a rate of infusion, then diabetes must be strongly suspected.

In the four or five years following the discovery of insulin, in 1922, a large number of publications were concerned with the usefulness of insulin in surgical operations on nondiabetic patients. Treatment with insulin and dextrose was heralded by some as a *specific in the treatment of surgical shock and post-operative acidosis*. Early work which was thought to indicate diminished amounts of insulin in the tissues of dogs that had been subjected to ether anesthesia apparently provided a sound basis for the belief that insulin might be a valuable agent in post-operative treatment. Now, however, it is known that early assays of insulin in animal tissues other than the pancreas were errone-

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CHAPTER XIII

GENITO-URINARY AND GYNECOLOGIC COMPLICATIONS OF DIABETES

DISEASES OF THE BLADDER, URETERS AND KIDNEY

In severe diabetes with ineffective control, lowered resistance to infection favors development of infection of the urinary tract. Cystitis and pyelonephritis were much more common in the Naunyn era than, to judge from our experience, is now the case. Also, as Naunyn emphasized, the saccharine urine provided a favorable medium for the growth of yeasts and resulted in much balanitis, vaginitis and cystitis. In such cases the urine in the bladder might undergo fermentation leading to pneumaturia A number of references to pneumaturia were cited by Naunyn. In one such case the gas was inflammable and contained not only carbon dioxide but methane and hydrogen. In another the products were alcohol and carbon dioxide. Naunyn also was impressed with the frequent occurrence of impotence in diabetic men. The evidence indicated that it was not dependent on destruction of spermatozoa

The occurrence of cord bladder among patients with diabetes receives consideration in Chapter XVIII. Postmortem examination in one of two cases of cord bladder reported by Gill in which syphilis was excluded revealed degeneration in the posterior columns of the spinal cord.

Armani described a hyaline vacuolization of the epithelium of Henle's loops in the kidneys, which Ehrlich in 1883 found to be due to deposits of glycogen. This lesion is unassociated with symptoms, but is regarded by pathologists as almost pathognomonic of diabetes.[1] Treatment with insulin, as was pointed out by

[1] Warren cited Gierke's finding of glycogenic infiltration of the epithelium of Henle's loops not only in clinical and pancreatic diabetes, but also after extirpation of the celiac plexus and in phlorhizin poisoning In the first three instances the level of blood sugar was increased, in the last it was normal or low The point in common was the presence of dextrose in the urine

In the presence of diabetes glycogen occurs with less regularity in the glomeruli and convoluted tubules Other less constant abnormal glycogen deposits associated with diabetes are in fibers of the heart muscle and in the leukocytes

Warren and Root, reduces the amount of hyaline vacuolization, and in many cases in which treatment has been effective none can be found. Tubular degeneration of the kidneys from acidosis is referred to elsewhere (see Chapter X). It is responsible for the albuminuria and cylindruria (coma casts) encountered in the presence of acidosis.

An unusual and little recognized syndrome of diabetes, hypertension and albuminuria has been described by Kimmelstiel and Wilson and by Anson. The diabetes is usually mild. The hypertension is associated with retinal hemorrhage and edema. The nephrotic syndrome depends on the extent and duration of the albuminuria. The pathogenesis is said to depend on severe and extensive arteriolar degeneration associated with and perhaps resulting in diabetes mellitus, hypertension and renal damage. The condition has been named "*intercapillary glomerulosclerosis*" A group of four cases in which the lesions of intercapillary glomerulosclerosis were observed at necropsy is reported in detail by Newburger and Peters. Reasons for regarding the condition as a disease entity are given.

Arteriosclerotic disease of the kidneys occurs with no greater frequency in diabetic patients than in others (see Chapter XXII).

The urologic complications encountered among about 4500 diabetic patients seen in The Mayo Clinic between January 1, 1934 and December 31, 1938 have been reviewed by Pool. Minor disturbances such as prostatitis accounted for 125 cases; balanitis, phimosis and pruritus were not encountered among male patients. Pruritus or vaginitis in females is to be considered later. Two hundred and seventeen patients, representing only about 4 per cent of all diabetic patients seen during these years required special treatment from the Section on Urology. Some surgical procedure was resorted to in 153 of these 217 cases The type of operation and the attendant mortality are shown in Table 4.

Sixty-four of the nonsurgical patients with diabetes suffered from infection of the urinary tract In sixteen cases the infection was acute, in forty eight chronic. In addition there were two cases of acute gonorrheal infection, and three of acute and one of chronic nonspecific epididymitis.

Of the sixteen cases of acute infection, acute pyelonephritis was the diagnosis in eleven and infection lower in the urinary

TABLE 4

UROLOGIC OPERATIONS IN CASES OF DIABETES (1934–1938)

	Number	Deaths
Transurethral prostatic resection	97	4*
Nephrectomy	14	1†
[illegible]	9	1‡
[illegible]	2	
[illegible]	1	
[illegible]	1	1§
[illegible]	1	
[illegible]	1	
[illegible]	4	
[illegible]	2	
[illegible]	4	
[illegible]	1	
[illegible]	1	
[illegible]	1	
[illegible]	1	
[illegible]	1	
[illegible]	1	
Circumcision	2	
Operation for vesical overdistention	1	
Plastic operation on penis	1	
Simple amputation of penis	1	
Incision and excision of hydrocele	2	
Orchidectomy	3	
Exploration for bilateral spermatocele	1	
Total	153	7

* The average age of the patients subjected to transurethral prostatectomy was sixty-seven years, the oldest patient was ninety years old, and thirty-three of the ninety-seven were more than seventy One of the four postoperative deaths was from bronchopneumonia, one from pulmonary embolism, one from anuria and uremia, cause undetermined, and one from infection by hemolytic streptococcus

† The patient was fifty-four years of age The cause of death in his case was pneumonia

‡ The death followed a ureterolithotomy The patient was fifty-one years of age A paralytic ileus ultimately leading to peritonitis was responsible

§ The patient in the case of bilateral ureterosigmoidostomy suffered from extensive carcinoma of the bladder

tract in five. The infecting organism in ten of these cases was the Escherichia coli, in two it was Staphylococcus aureus, in two Proteus ammoniæ, and in one both Escherichia coli and a gram-positive coccus In one the organism was not determined.

The treatment of these cases was varied Three patients were given some form of mandelic acid, six received sulfanilamide, three received a ketogenic diet. The results were good in thirteen of the sixteen cases, poor in three. Those patients who recovered seemed to respond to the treatment given as well as would have been expected of similarly infected patients without diabetes Of the three patients who failed to respond two died, infection was

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Operations on ureter and kidney other than nephrectomy	9	1‡
Transurethral manipulation of ureteral calculus	2	
Nephrostomy for anuria	1	
Bilateral ureterosigmoidostomy	1	1§
Rovsing operation for polycystic disease	1	
Exploration of kidney for calculus	1	
Urethral caruncle.	4	
[illegible]	2	
[illegible]	4	
[illegible]	1	
[illegible]	1	
[illegible]	1	
[illegible]	1	
[illegible]	1	
[illegible]	1	
Circumcision	2	
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[illegible]	1	1§
[illegible]	1	
[illegible]	1	
[illegible]	4	
Operation for abscess of prostatic duct	2	
Transurethral removal and fulguration of vesical tumor	4	
Internal urethrotomy	1	
Segmental resection of bladder tumor	1	
Transurethral removal of scar tissue from bladder neck	1	
Incision of periurethral abscess	1	
Excision perineal fistula	1	
Linear fulguration of urethra, female	1	
Circumcision	2	
Operation for vesical overdistention	1	
Plastic operation on penis	1	
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responsible for the death of both. In the third case pyuria persisted despite intensive treatment with both elixir of ammonium mandelate and sulfanilamide.

In the group of forty-eight cases of chronic urinary infection the Escherichia coli also predominated as the infective organism, streptococci were present in only two cases and staphylococci in only one. Forty of these patients responded well to the treatment given.

So far as could be determined mandelic acid and sulfanilamide were as well tolerated by these diabetic patients as by other patients. Neither drug seemed to affect either tolerance for carbohydrate or sensitivity to insulin. In two cases a ketogenic diet was given with satisfactory results and without ill-effect, and in three others combined treatment with this diet and mandelic acid was effective and harmless. In cases with gonorrheal infection fever therapy has been used, also without harm.

This clinical experience differs, as would be expected, from that based on findings at necropsy, such as has been reported by Sharkey and Root. Evidence of infection of the urinary tract with virulent organisms of the staphylococcic and streptococcic groups was obtained by them in 18 per cent of 196 diabetic necropsies. In twenty-five or about 70 per cent of these cases the infection of the urinary tract was hematogenous and secondary to infections elsewhere. Ascending infection secondary to ureteral obstruction had occurred in five cases, and in five more no etiologic factor could be demonstrated. They emphasized the striking paucity of symptoms referable to the urinary tract in many of these cases, and advised that the occurrence of unexplained fever among diabetic patients should prompt investigation of the possibility of such infection.

GYNECOLOGIC COMPLICATIONS

There is nothing to prevent any of the diseases of the female organs of generation from occurring among diabetic women, but certain gynecologic conditions may be regarded as secondary to, or resulting from, the metabolic abnormalities of diabetes. In particular, they are pruritus with or without inflammatory lesions of the perineum, vulva and vagina, dysmenorrhea and amenorrhea.

Pruritus.—Pruritus of the pudenda is a rather common complication among diabetic women. It was present in 20 per cent of the new cases in which diabetes was observed among women at the clinic; the condition was accompanied by vulvitis in a third, and by vaginitis in a sixth of these cases. These lesions affect by preference patients who are more or less obese and occur somewhat independently of the intensity of the diabetes. Bokelmann made tests of the glucose tolerance of ten women suffering from pruritus who did not have glycosuria and had not been considered to have diabetes previously. All of them gave responses that were typical of diabetes mellitus. At the same time, in the out-patient clinic of the Charité, twelve of twenty-six patients who had eczema of the vulva were excreting sugar. To neglect examination of the urine in cases of this kind is inexcusable. The degree of suffering is incredible. Naunyn spoke of pruritus of the vulva as one of the most harrowing symptoms of diabetes which may lead to self-destruction, yet patients are seen repeatedly who have come from examinations by gynecologists without having learned of the existence of diabetes.

The itching in the genital pruritus of diabetes first affects the inner and outer surfaces of the labia minora and spreads to the adjacent parts that are moistened by the saccharine urine. Von Noorden and Isaac, Perazzi and others found that the mycelia of various fungi play a considerable part at times and that they actually penetrate the epithelium. The skin moistened with a solution of sugar affords an excellent culture medium. The inflammation attributable to the growth of these organisms and to scratching with the fingers can be limited to superficial dermatitis or can lead to furuncles and phlegmons. Uncleanliness aggravates the condition The infection usually is trichophytosis. In other cases, particularly those in which the patients are overnervous women, there may be no infection but local toxic pruritus analogous to the more generalized pruritus of diabetes

The treatment of these conditions is completely ineffective until glycosuria has been eliminated Local treatment with precipitated sulfur 2 parts, salicylic acid 2 parts and benzoated lard 30 parts has been recommended Von Noorden and Isaac used 10 per cent anesthesin (ethyl aminobenzoate with cocaine) and 5 per cent calcium chloride ointment and gave salicylates by mouth

Personal experience indicates that satisfactory treatment of the diabetes usually is all that is necessary; this leads to the conclusion that whatever organisms are usually concerned must be relatively harmless except as their growth is facilitated by glycosuria. Von Noorden and Isaac warned against roentgen irradiation.

Menstrual irregularity.—With untreated or poorly treated diabetes, amenorrhea and menstrual irregularity are common. The premature cessation of the menses was given as a complaint in 124 of 746 new cases of diabetes among women who were observed at The Mayo Clinic in the four-year period, 1923 to 1926 inclusive, and irregularity was reported in fifty-seven other cases. In the next four years the figures for these complaints fell to thirty-five and eighteen, respectively, although the number of new patients remained approximately the same. In the first period only 9 3 per cent of the new patients had had insulin, whereas in the second period 26 per cent had been treated with it. The general care, presumably, had been improved correspondingly. When insulin is used correctly and the diet is arranged to supply all the requirements of adequate nutrition, the menses of otherwise normal diabetic women are perfectly normal. We have had almost no cases of failure to establish regular menstruation in girls under treatment at puberty, and with older girls and women whose menses have ceased prematurely with the development of diabetes, the prompt re-establishment of the normal menstrual cycle has been the rule. *The diabetes must be controlled and particular attention must be paid to the provision in the diet for adequate allowances of protein, all necessary vitamins, calcium, iron and calories.*

It was the opinion of Lecorché that the food tolerance in diabetes is improved by menstruation. Naunyn's experience pointed otherwise, and von Noorden and Isaac noted increased glycosuria in 20 per cent of their cases. Harrop and Mosenthal reported a case in which coma developed, followed by improvement in the interval, and then by fatal coma at the next menstrual period. This menstrual effect was attributed by Rosenbloom to the influence of the heightened emotional status of the menstrual periods, whereas Küstner attributed it to a depression of the renal threshold for sugar in menstruation, analogous to that observed in pregnancy. The matter seems to be of minor significance, since whatever

the change it is seldom sufficient to affect the dosage of insulin required by well-trained patients.

Loss of libido—Loss of sex interest was reported by less than 5 per cent of the women observed at the clinic between 1923 and 1926 Von Noorden and Isaac stated that the depression of libido is almost always considerable in severe diabetes, to the point sometimes of direct disgust at intercourse, but that in cases of mild diabetes sexual irritability may be increased even in the absence of pruritus vulvæ. The potency of the completely depancreatized dog persists when insulin is given, and there is nothing in clinical experience to indicate that this is not true of well-treated human patients, both male and female

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CHAPTER XIV

PREGNANCY COMPLICATING DIABETES

Pregnancy among patients with diabetes is a subject demanding the closest attention of internist and obstetrician. It was estimated by Joslin in 1928 that there then were more than 100,000 diabetic women of childbearing age in the United States. This number has been steadily augmented by diabetic children who have reached the age of maturity. The fertility of these women also is enhanced by improved methods of diabetic management.

According to Williams the maternal mortality of diabetic women in the Johns Hopkins Hospital during pregnancy or at delivery, prior to the discovery of insulin, was from 25 to 30 per cent. The risk is much less now. However, White reported the maternal death rate in cases of diabetes in the Deaconess Hospital to be 3 8 per cent, or six times greater than that for nondiabetic patients, and in 118 cases collected by Skipper it was 9 3 per cent In his own series of thirty-three cases none of the patients died These statistics apply to patients receiving superior care. Still more serious has been the fetal mortality. Prepartum, intrapartum and postpartum deaths of the infants born of diabetic women continued at from 25 to 40 per cent of all pregnancies, that is, with almost as great a frequency as in the era before insulin, until in The Mayo Clinic and in the Deaconess Hospital appreciation came that these pregnancies must be terminated early by cesarean section, and that the infants after delivery must receive special attention to prevent their deaths from hypoglycemic convulsions and asphyxia.

DIAGNOSIS OF DIABETES IN PREGNANCY

In most cases of pregnancy complicating diabetes, the diabetes has existed before the pregnancy; in some cases, however, glycosuria is first discovered in the course of gestation and a problem of diagnosis then arises. Glycosuria alone does not establish the presence of diabetes, especially during pregnancy, and even the presence of acetone bodies in the urine may have little significance if the patient is starved or vomiting. Yet proper evaluation of

glycosuria, with or without accompanying ketosis, is of major importance, since diabetes is a complication of extreme gravity, whereas the simple glycosuria of pregnancy is relatively harmless The different significance of these two conditions has been apparent since it was recognized by Lecorché in 1885, but the development of clinical methods for measuring the concentration of blood sugar was necessary before reliable distinction became possible. If the value for the blood sugar exceeds 0.120 gm. per 100 c.c when the patient is fasting, the diagnosis of diabetes is established. If the value is less than this, further examination is indicated; namely, a sugar tolerance test (see Chapter II). The simple glycosuria of pregnancy occurs with a normal concentration of blood sugar and differs from renal glycosuria only in its impermanence. It appears after the first month of gestation and leaves soon after term. The phenomenon was first described by Maase in 1911. It could be demonstrated so consistently among pregnant women by Mann that Frank and Nothmann proposed a test for early pregnancy based on it The depression of the renal threshold is usually of a moderate degree so that the urine only contains sugar after the ingestion of sugar and irregularly after meals rich in carbohydrate.

The harmlessness of the normoglycemic glycosuria of pregnancy is questioned by several authorities. In a case of ours the patient had glycosuria with a normal flat blood sugar time curve in one pregnancy, but true diabetes developed and insulin was required for its control in the following pregnancy. Furthermore, many cases of true severe diabetes have been encountered in which the disease began in the course of pregnancy and was neglected because the significance of the sugar in the urine was underestimated. This is bad practice. It should be made a rule by every obstetrician to hold patients who have glycosuria under supervision until the possibility of diabetes has been excluded by a sugar tolerance test performed three months after delivery

Lactosuria also may lead to diagnostic confusion. It occurs late in pregnancy and usually not until after delivery: (1) before the infant is taking much, if any, milk from the breasts, (2) if mothers are not permitted to nurse, and (3) if the supply of milk is larger than is required. Lactose, reabsorbed from the breasts under the conditions mentioned, is not utilizable and is

excreted in the urine. Lactose gives a positive result on test for sugar with Benedict's solution but is not fermented by yeast. Its contribution to the reducing power of urine can be determined by analyzing the urine for sugar before and after subjecting it to fermentation. A 100 c.c. specimen with which a cake of fresh bakers' yeast has been mixed will lose all reducing power owing to dextrose after standing in a warm room overnight.

MATERNAL ACCIDENTS

Acidosis is the complication most to be feared in pregnancies of diabetic women. In the era before insulin it was the principal cause of maternal mortality, although infection also took many lives. The total metabolism is elevated by the growth of the fetus, glycogen stores are likely to be depleted if any toxemia develops and diabetic control with insulin is made more difficult by fluctuations in tolerance and the changing requirements for insulin which will be described. In the White-Joslin series the carbon dioxide combining power of the plasma was low in seventeen cases, in seven of these the patients had clinical signs of coma. The value for the blood sugar was not proportionately elevated.

Toxemia was recognized in 12 per cent of the cases in the White-Joslin series and the incidence of eclampsia was 5 per cent, compared with an average of 0.3 per cent for nondiabetics. An endocrine imbalance was considered responsible. Monthly determinations of the concentration of prolan and estrin in the urine revealed elevation of placental prolan in nine of fifteen cases. Toxemia developed in six of those in which the concentration of prolan was high. A compensatory rise in the concentration of estrin occurred in two cases in which the value for the prolan was high. A rise in the value for the prolan and a fall in the concentration of estrin from the sixth month on preceded toxemia without fail. The determinations were made by Smith and Smith, who previously had demonstrated that an excess of placental prolan occurred prior to the onset of toxemia in nondiabetics.[1]

[1] In this connection White called attention to work by Snyder and Hoopes which demonstrated that injection of prolan into pregnant rats and rabbits had effects similar to those encountered in diabetic pregnancies, namely overdevelopment, death and maceration of giant fetuses

A factor of primary importance in the production of a condition simulating what is called toxemia of pregnancy is nutritional deficiency. The experimentalists have shown that the requirement for vitamin B_1 is increased from three to five times in normal pregnant animals, and if diabetes still further augments the requirement for this vitamin, as is supposed, another explanation is suggested for the high incidence of conditions resembling toxemia in pregnant diabetic women. According to Strauss and McDonald hyperemesis in some cases of pregnancy has been cured by giving generous doses of yeast or by administration of crystalline thiamin chloride. In a case reported from The Mayo Clinic by Randall and Wagener, glycosuria, albuminuria, hemorrhagic retinitis with edema of the optic disks, subjective disturbances of vision and mental cloudiness were corrected by such treatment, and since then equally dramatic results have been obtained in many other cases. When one sees those results, one wonders how many women have died for lack of an adequate diet.

Precocious vomiting was encountered only once in the White-Joslin series and extra-uterine pregnancy once. Premature separation of the placenta did not occur. There were two cases of abscess of the breast and three cases of puerperal sepsis. Hydramnion was met with in only four cases, although by others it has been said to be of frequent occurrence in the pregnancies of diabetic women. It has been attributed to fetal diuresis provoked by hyperglycemia. In a case reported by Labbé and Couvelaire hydramnion would develop whenever the patient neglected the diet and disappear again on return to the strict regimen.

Changing insulin requirements in pregnancy.—The tolerance for sugar is likely to be decreased in the first trimester of pregnancy, so that patients who are under satisfactory management require larger doses of insulin than were needed before conception. This observation was made in three of the cases reported by Parsons and me and has been evident in later cases. It partly may be explained in the early months on the basis of unusual metabolic conditions. In the later months the tolerance also may continue to be depressed, although usually in the last trimester it increases, sometimes to the point where no insulin is required. Several of the cases in the 1928 Mayo Clinic report (Wilder and Parsons) and six of White and Joslin's cases illustrated such im

proving tolerance. The observation is in accordance with the results of experiments of Carlson and Ginsburg, which were fully confirmed later by Cuthbert, Ivy, Isaacs and Gray. When pregnant diabetic dogs were depancreatized, diabetes either was mild or failed to develop until after the birth of the puppies, and the supposition is that the fetal pancreas is able to supply the mother with insulin.[2] The subject is not without practical significance. Unless the patient is warned against the possible necessity at this time of lowering her doses of insulin, severe reactions may occur and threaten both her life and that of her child.

The depression of the renal threshold by pregnancy (see p. 234) in patients with established diabetes adds to the difficulty of management. With a low threshold it is hazardous to give enough insulin to suppress glycosuria, because a sugar-free urine under such circumstances is likely to represent a level of blood sugar which is below normal and possibly dangerously so. Therefore, in pregnant diabetic women, unless facilities are at hand for frequent determinations of the concentration of blood sugar, it is safer to regulate management so that the urine at all times will contain a trace of sugar.

Lactation.—Lactose in the urine, by being mistaken for dextrose (see p. 234), may prompt excessive administration of insulin, especially during the first few days of the puerperium At this time the patient's requirement for insulin is likely to be diminished, as was found by Allan in observations on depancreatized dogs treated with insulin (Macleod). The improved tolerance is then explained by the transference of sugar from the blood to the breasts for conversion into galactose and lactose. There is no objection to having the diabetic mother nurse her child. The majority of our patients, like those reported from the Johns Hopkins Hospital by Peckham, have done so in whole or in part.[3]

[2] Pack and Barber answered those critics who doubted the permeability of the placenta to insulin by injecting insulin into the fetuses of goats and observing a decrease in the concentration of maternal blood sugar Britton, reversing the procedure, injected insulin into a pregnant cat and obtained a decrease in the value [illegible]

[illegible]

tion, since lactation depends on preparation of the mammary glands by estrin and stimulation after delivery by a specific lactogenic hormone. Another possible ex-

FETAL ACCIDENTS

Congenital defects are said to occur with greater frequency among children of diabetic mothers. In the 208 cases of pregnancy complicating diabetes in the Joslin clinic, White found seven abnormal babies. The incidence of defects among stillbirths was one in seven, compared to one in sixty-one for the consecutive pregnancies of nondiabetic women at the Johns Hopkins Hospital, as reported by Dippel.

The large size of babies of diabetic mothers frequently is commented on. "Riesenkinder," the Germans called them. We have not encountered the abnormality, possibly because in an earlier series of cases the diets used were low in carbohydrate and in recent years we have delivered the child by cesarean section between the thirty-sixth and thirty-seventh week. Another possible explanation has been our insistence on a diet richly supplied with vitamins and calcium. A large, flabby (edematous) fetus possibly is an effect of nutritional deficiency of the mother. It is not improbable that a relative lack of vitamin B_1 is responsible.

Stillbirths, prematurely and at term, occur more frequently with diabetic patients. These we also have largely avoided recently, in part because we have delivered the babies early by cesarean section.

The principal difficulty that we formerly encountered was the death of the infant soon after birth. The usual cause in my opinion frequently was hypoglycemia. I have referred to the evidence that the pancreas of the fetus in diabetes meets the maternal demand for insulin during the later months of pregnancy. If this occurs the child when born possesses an islet mechanism tuned up to an activity exceeding that required by the infant alone. At times the manifestation of this can be found at necropsy, in the form of hyperplasia of the islands of Langerhans, as was demonstrated first by Dubreuil and Anderodias. Parsons, Randall and I called attention to the subject in 1926 and 1928 and recommended early feeding of the infant. My interest in it became acute in 1933 as a result of experience with a case later reported by Randall and Rynearson.

planation in some cases may be a requirement for a larger intake of thiamin or other vitamins than the diet has provided Production of milk in the period of lactation is reported by Tarr and McNeile to have been increased by abundant administration of vitamin B concentrates

Briefly, the child was delivered by cesarean section and, anticipating hypoglycemia, I made preparation to observe it continuously myself, to obtain repeated analyses of capillary blood and to give dextrose parenterally if hypoglycemia was encountered. The mother, aged twenty five years, had been under our care for several years after the onset of her diabetes eight years before She had been pregnant three times before. Once a miscarriage had occurred after thirty weeks of gestation, and twice she had been delivered at about the thirty fourth week of pregnancy One of the infants had been dead at birth, but two had been born alive and had died of some unknown cause The baby born from the fourth gestation had convulsive movements sixty-eight minutes after its delivery and the value for the blood sugar then was 0 043 gm per 100 c.c. A subcutaneous injection of dextrose was given and the convulsive movements stopped Later, repeated oral feedings sufficient to prevent a recurrence of hypoglycemic symptoms were given and the baby lived. He is a six-year-old healthy boy at this writing

Our experience with the surviving children of diabetic women has been entirely satisfactory. So far as we are informed not one of them has yet developed diabetes

TREATMENT OF THE MOTHER DURING PREGNANCY

Mention already has been made of the importance of obtaining optimal nutrition. In these days of vitamin concentrates adequacy of vitamins should be insured by supplementing the diet with cod liver oil or equivalents, brewers' yeast and thiamin chloride. It also is well to prescribe calcium phosphate unless the consumption of milk is not less than 1 liter daily. Specimens of urine are to be tested for sugar before each meal and at bed time, and with due consideration to the possibility of a low renal threshold, unmodified insulin or solution of zinc insulin crystals should be given frequently in small doses It is not undesirable to use protamine-zinc insulin in these cases, but the dose of it, given once daily before breakfast, should be small enough so that the specimen of urine obtained before breakfast will contain a trace of sugar. Hypoglycemia is to be avoided at all costs, and the possibility of fluctuation in insulin requirement is to be held in mind.

THE DELIVERY AND CARE OF THE INFANT

By adopting the procedure mentioned in connection with the case I referred to previously (see above), since 1933 we have had successful deliveries in many successive cases The first

eight of these were reported by Randall and Rynearson. Cesarean section is performed in the thirty-sixth or thirty-seventh week of pregnancy, at which time sterilization by ligation of the fallopian tubes can be effected if permitted.[4] Following the delivery of the child, efforts are directed immediately to prevent hypoglycemia and to combat asphyxia. Care is taken to be certain that the pharynx and trachea are free of mucus and amniotic fluid, by keeping the head dependent, and if necessary, by aspirating with a tracheal catheter. Occasionally inhalation of carbon dioxide and oxygen is needed to establish respiration. When the baby is breathing, it is placed in a Hess incubator equipped with a cover and connected with an oxygen tank. Flow of oxygen is regulated in order to maintain an oxygen concentration of 40 to 50 per cent for the first few hours. The temperature of the incubator is maintained at 85° F. Five cubic centimeters of a 10 per cent solution of dextrose is administered into each buttock. Further injections of 10 c.c. of a 10 per cent solution of dextrose are given at intervals of two to three hours; the interval is regulated by the value for the blood sugar as determined by the micromethod, by the behavior of the infant and by the ability of the infant to take feedings by mouth.

Feeding is attempted within four hours. Ten cubic centimeters of a 10 per cent solution of dextrose or 7 c.c. of Marriott's lactic acid-karo mixture is given every two hours for the first

[4] By cesarean section the child can be spared not only those dangers to which it is exposed in the uterus during the last weeks of pregnancy, but also the fatigue of labor and the possibility of injury during labor from trauma, asphyxia or the hypoglycemia induced by the exertion of labor. White also advocated cesarean section in diabetic pregnancies. She wrote: "Prolonged, difficult labor, normal or induced, has disadvantages for the diabetic. Those of immediate importance are the early exhaustion of the glycogen reserve and the danger of sepsis, the danger of hyper-insulinism, exogenous and endogenous, and the danger of acidosis. The secondary considerations are the added handicap of a torn perineum or cervix and consequent indication for later surgery. These patients are not physically fit for numerous pregnancies. The baby has not the vitality of the child of the non diabetic, and consequently the risk is great of injury from long labor to this large overdeveloped, but at the same time, flabby child. Furthermore, the induction of labor does not answer the problem as well as cesarean section because induction of labor is not safe until the cervix is soft, and the cervix may not be soft until after the baby has died . . .

"Prolonged narcosis in the presence of low alkali reserve and glycogen depletion is a perfect setting for the onset of true diabetic coma. Everywhere it is evident that 'the modern woman demands safe labor, freedom from unnecessary pain, a reasonable length of labor, and a complete restitution. . . .' In our opinion the diabetic deserves not less."

forty-eight hours if it can be tolerated.[5] Then 30 c.c. of lactic acid-Karo mixture is given every three hours. Sufficient nursing assistance is secured to permit uninterrupted observation of the infant for the first forty-eight to seventy-two hours. Whenever the feeding is poorly taken or whenever twitchings, convulsive movements or cyanosis suggests the development of hypoglycemia, 10 c.c. of a 10 per cent solution of dextrose is given orally if possible, or intramuscularly.

The length of the period of danger from the complications of hypoglycemia cannot be predicted with accuracy. In one case it was necessary to administer dextrose parenterally every two hours for three days because of regurgitation of the formula. The concentration of oxygen in the incubator gradually is diminished, and when the color of the infant remains normal in the ordinary atmosphere, administration of oxygen is discontinued. Great difficulties were encountered in the following case, one of those reported from The Mayo Clinic in 1936 by Randall and Rynearson.

The mother was thirty years of age, having had diabetes for seven years. Delivery was by cesarean section. The infant, a girl weighing 2,990 gm was born at 9 a.m., February 12, 1936. The values for the mother's blood sugar before and after the operation were 0.142 and 0.234 gm. per 100 c.c. Blood fro[illegible]
the value [illegible]
0.099 gm [illegible]
respiratio[illegible]
10 per cent solution of dextrose was injected into each buttock and the baby was placed in an incubator in which the oxygen tension was kept at 50 per cent. At noon, 10 c.c. of a 10 per cent solution of dextrose was injected into the buttocks and the child was given some water by mouth. Just before the feeding at 3 p.m. the value for the infant's blood sugar, as determined by the [illegible]

[illegible]

improved and the feeding was finished. A 10 per cent solution of dextrose was administered intramuscularly at 5 and 7 p.m. At 9 o'clock the value for blood sugar was found to be 0.059 gm. per 100 c.c. At 9.30 p.m. the child received another intramuscular injection of the solution of dextrose and an-

[5] The formula for this mixture calls for 70 gm. of Karo syrup and 930 c.c. of whole milk. These are mixed and boiled for fifteen minutes. The mixture is then [illegible] solution of lactic acid [illegible] should be taken not to [illegible] All the paraphernalia [illegible]

other feeding of the formula. During the first night efforts were made to feed the child by mouth with the formula and 10 per cent solution of dextrose, but both were regurgitated and it was necessary to administer a 10 per cent solution of dextrose intramuscularly every two hours

Lack of space prevents the detailed report of the child's condition and the treatment, but at noon of the second day of life, muscular twitchings occurred. These were followed in an hour by a mild convulsive seizure and cyanosis Five cubic centimeters of a 10 per cent solution of dextrose was injected into the peritoneal cavity and the condition improved. After this treatment the value for the blood sugar was found to be 0.187 gm. per 100 c c. During the second night and the third day the muscular twitchings were prominent and because of the continued regurgitation of feedings by mouth the child was given intramuscular injections of a 10 per cent solution of dextrose At 5 p m on the third day the value for the blood sugar was still low, 0 066 gm per 100 c.c. During the third night and the fourth day she retained the feedings and the muscular twitchings were much less frequent than they had been Intramuscular injections were no longer necessary and [illegible] After the fourth day [illegible] mally On

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CHAPTER XV

DISEASES OF THE THYROID GLAND COMPLICATING DIABETES

Hyperthyroidism was primarily responsible for precipitati acidosis in six of the 108 instances of diabetic coma review in the clinic by Baker. In many more cases of diabetes with l severe acidosis it has given us serious concern. In the pre-insul era it usually constituted a fatal complication. Sattler, in h monograph published in 1909, collected fifty-six reports of cas in which diabetes was associated with toxic goiter. In thirty-seve cases sufficient time had elapsed to afford information on pro nosis and in twenty-five of these cases the disease ended fatal in a comparatively short time. Fitz in 1921, in the records o the Massachusetts General Hospital and in those of The May Clinic, found thirty-nine cases of diabetes complicated by thyroi disease. In many the goiter was nontoxic, a condition which h found to be without influence on the course of diabetes. In th others it was toxic and in twelve of these cases follow-up dat were obtained. Two of the three patients who were not operated on died of diabetes, one in ten days and another in less than three months The third was failing rapidly after ten months Only four of the nine patients subjected to one or another of the various operative procedures then employed—injection of hot water, ligation of thyroid vessels, and so forth—survived longer than a few months.

THE THYROID GLAND AND CARBOHYDRATE METABOLISM

When urines are examined daily in a large goiter service mild degrees of glycosuria are frequently encountered,[1] and if patients with hyperthyroidism are given a test meal of 50 to 100 gm. of dextrose abnormal blood sugar time curves frequently are obtained. These curves seem to be characterized by high normal blood sugar values for the zero hour (0 120 to 0.140 gm. for each

[1] Joslin reported glycosuria in 38 6 per cent of cases of "primary hyperthyroidism" and in 27 7 per cent of cases of "secondary hyperthyroidism"

100 c.c. of blood), abnormally high values at thirty minutes after the dextrose is ingested (often exceeding 0 200 gm.) and normal values later. Also the injection of dextrose by vein in cases of hyperthyroidism reveals abnormalities (Wilder and Sansum). Healthy normal human subjects will accept continuous injections of dextrose at a rate of 0.8 gm. per kilogram of body weight per hour without passing sugar in the urine; patients with hyperthyroidism excrete sugar when the rate of injection is only 0 6 gm. or less per kilogram per hour.

These several observations show that the utilization of dextrose frequently is disturbed in cases of hyperthyroidism; they do not prove either that the capacity of the pancreas to supply insulin is at fault or that oxidation is disturbed Therefore, to my mind, they do not establish the existence of a state of diabetes. The spontaneous glycosuria encountered is not severe. After the hyperthyroidism has been corrected by thyroidectomy or otherwise, normal blood sugar time curves are obtained, and so far as has been determined, persistent glycosuria (diabetes) seldom develops at a later date.

Evidence from respiratory quotients indicates that oxidation of glucose proceeds as well as, or even better, than normally in cases of hyperthyroidism. In cases of exophthalmic goiter the respiratory quotient was found by Du Bois to rise more abruptly than normal after the ingestion of test meals of dextrose, an observation that has been repeatedly confirmed in our laboratories and elsewhere[2] The glycosuria encountered in these cases is definitely set apart from that of diabetes mellitus by this response of the respiratory quotient, because in true diabetes the rise of the quotient after ingestion of dextrose is usually sluggish, and in cases of severe diabetes no response at all is obtained

Thyroid extract when fed to normal persons occasionally, but by no means always, provokes an alimentary type of glycosuria comparable to that observed in some cases of spontaneous hyperthyroidism.[3] On the other hand, when thyroid extract is given

[3] Mirsky and Broh Kahn in eviscerated and nephrectomized rabbits previously made hyperthyroid [illegible]

to patients with diabetes a marked intensification of glycosuria occurs and persists for some time after the administration of the drug is discontinued. Grawitz reported such an experiment with results that I have confirmed. In a case of mild diabetes in which good control was obtained by diet without the use of insulin, I gave 3 gm. of desiccated thyroid glands in a period of nine days. This elevated the basal metabolic rate from an average level of —7 per cent to a maximal level of +20 per cent, and although the food ingested remained the same, sugar appeared in the urine in large amounts. When the administration of the drug was discontinued, glycosuria persisted to such an extent that restriction of the diet and administration of insulin were necessary to control it, and only later, after the basal metabolism had again fallen to normal, was the previous good tolerance regained. This experiment has been reported before (Wilder, December, 1926).

These and other experimental as well as clinical observations support the opinion that the effect of hyperthyroidism on carbohydrate metabolism is dual. On the one hand there is an adrenergic-like action which interferes with the storage of glycogen or releases glycogen previously stored by the liver; on the other hand, there is an antagonism to the action of insulin. When severe clinical diabetes is complicated by hyperthyroidism the requirement for exogenous (injected) insulin usually is very greatly increased, and from this it is reasonable to suppose that the pancreas of the nondiabetic patient must indirectly be stimulated by hyperthyroidism to provide a comparably large supply of insulin.[4] In the nondiabetic patient who has hyperthyroidism, to judge from the behavior of respiratory quotients, the supply

[4] Glaser noted hydropic degeneration and atrophy in the pancreatic islands of mice after continued injections of thyroxin, which is evidence of exhaustion by [illegible]

[illegible] of exophthalmic goiter [illegible] tologic changes in the [illegible] hyperthyroidism [illegible] the other hand, hyperplasia of [illegible] omy in animals by Tatum, as

from the pancreas is increased enough to maintain normal rates of oxidation of dextrose, but even with adequate insulin complete stabilization of hepatic glycogen, in the face of an hyperirritable sympathetic nervous system, may be impossible. This, to my mind, is the only satisfactory explanation for the frequency of transient alimentary glycosuria in cases of hyperthyroidism and for the relative infrequency of true diabetes.

DIAGNOSIS OF ASSOCIATED DIABETES AND HYPERTHYROIDISM

The diagnosis of hyperthyroidism today is based on the presence of a basal metabolic rate which is 20 per cent or more above normal and not otherwise explained, or, in exceptional cases with lower basal metabolic rates, on the presence of other characteristic symptoms. Adenomatous goiter with hyperthyroidism is distinguished from exophthalmic goiter by the criteria established by H. S. Plummer. The recognition of mild grades of hyperthyroidism is often a difficult matter, and in the presence of uncontrolled diabetes it becomes doubly difficult owing to the fact that certain symptoms, notably bulimia, loss of weight and weakness, are common to both diseases. It should be remembered that the normal metabolism of undernourished patients with controlled diabetes tends to be somewhat below the level called normal for fully nourished persons, and that the greater the degree of subnutrition the greater will be the discrepancy. Consequently a basal metabolic rate of +10 or +15 per cent, which would be considered as within the normal range for well-nourished persons, may represent in the case of an undernourished person a definite stimulation from hyperthyroidism. On the other hand, in the presence of severe diabetic acidosis the symptoms of grave hyperthyroidism may be so masked by those attributable to acidosis as easily to escape detection. The following case is illustrative:

A woman, aged forty years, was admitted to the hospital October 21, 1924, in deep diabetic coma with a carbon dioxide combining power 11 per cent by volume and blood sugar 0.400 gm per 100 c.c. Thyroidectomy had been performed in 1907 for exophthalmic goiter, but the general health had been good until recently. The patient had had two children in the interval and in 1921 had passed through a febrile condition thought to be encephalitis. Symptoms suggesting diabetes had developed abruptly in August, 1924.

During the year prior to this the body weight had increased 50 pounds (22.7 kg). In the next two months it declined 30 pounds (13.6 kg).

The thyroid gland was barely palpable and no thrill or bruit was detectable. Ocular symptoms were not pronounced; however, a faint tremor, the warmth and sweatiness of the skin, and tachycardia suggested the possibility of recurrent exophthalmic goiter. Consequently compound solution of iodine (Lugol's solution) was administered in addition to the more usual anticoma measures. The basal metabolic rate determined two days later was +38 per cent.

This patient was readmitted March 19, 1925, again with severe acidosis, the carbon dioxide combining power of the plasma being 10 per cent by

was not retained when given by mouth or by enema. After twenty-four hours, vomiting ceased and iodine again could be administered by mouth. The basal metabolic rate was not determined until March 25. It was then +47 per cent.

basal metabolic rate was determined on January 5; it was then +45 per cent. Thyroidectomy was performed January 12. The weight of the tissue removed was 22 gm. It showed hypertrophic parenchyma with regions of thyroiditis. The subsequent course was uneventful. At a later examination, April 18, 1926, the basal metabolic rate was −16 per cent, the diet had a glucose equivalent of 140 gm., and the insulin requirement was 40 units.

In a fatal case previously reported (Wilder, April, 1926) the patient was admitted in diabetic coma, and exophthalmic goiter was not suspected until the pathologist found hypertrophic parenchymatous tissue in the thyroid gland. The possibility of hyperthyroidism should therefore be borne in mind in every case of diabetic acidosis and, if suggestive symptoms, particularly tremor and marked tachycardia, are present, treatment should include the administration of iodine.[5]

management of diabetes and very conscientious. Yet she died at her home ... without having altered her regimen and without having acquired any infection or

Because of the frequency with which transient alimentary glycosuria and moderately elevated fasting blood sugar values are encountered in uncomplicated hyperthyroidism and because of the improbability that these abnormalities represent true diabetes mellitus, the diagnosis of diabetes, when hyperthyroidism is present, demands more rigid standards than otherwise. Post-absorptive values for venous blood sugar higher than 0.120 gm per 100 c.c. (by the Folin-Wu procedure) ordinarily can be accepted as diagnostic, but when hyperthyroidism is introduced this standard will be deceptive. Therefore, with Joslin, my colleagues and I have demanded, for a diagnosis of diabetes in cases of hyperthyroidism, a fasting value for blood sugar of 0.150 gm. per 100 c.c.

INCIDENCE OF ASSOCIATED DIABETES AND HYPERTHYROIDISM

Experience in this matter at The Mayo Clinic has twice been reviewed. The first study, made by me (December, 1926) covered the three years 1923, 1924 and 1925; the second, made with Regan, was for another three years, 1935 to 1937, inclusive. Comparison of the two periods provided information of some importance. It showed in the first place that the incidence of hyperthyroidism as a complication of diabetes declined from 3.1 per cent in the first period to 2.4 per cent in the second period. Nine years separated the two periods. In this interval the use of iodized salt became popularized for the prophylaxis of goiter and iodine was introduced in the treatment of exophthalmic goiter.

Other comparative data (Table 5) show further that the incidence of diabetes as a complication in all cases of hyperthyroidism increased from 1.1 per cent in the years 1923 to 1926 to 3.3 in the years 1935 to 1938. This was to be anticipated because in the twelve years that intervened the incidence of diabetic morbidity in the population as a whole had been mounting. The increase of diabetes as a complication of hyperthyroidism was noticeable, however, only in the cases of adenomatous goiter with hyperthyroidism. In them the figure for incidence of diabetes increased from 2.0 to 5.6 per cent, whereas for cases of exophthalmic goiter the highest incidence reached was only 1.7 per cent, and the latter figure is no greater than that for the frequency of diabetes

among all new registrations at The Mayo Clinic in 1937 (1.8 per cent).

I attribute the predilection of diabetes to cases of adenomatous goiter with hyperthyroidism to the fact that adenomatous goiter with hyperthyroidism is a disease usually of long duration. In contrast to exophthalmic goiter, the onset is insidious, severe nervous symptoms are absent and the recognition of disability by the patient is long postponed. In consequence, the pancreas is exposed for a longer period to excessive demands for insulin and greater opportunity is given for exhausting its insular reserve (see Chapter III).

TABLE 5

INCIDENCE OF COMBINED DIABETES AND HYPERTHYROIDISM JANUARY 1, 1923 TO JANUARY 1, 1926 AND JANUARY 1, 1935 TO JANUARY 1, 1938*

Disease	Cases.		Complicating disease	Cases.	Per cent of total.	Cases	Per cent of total.
	1923–26	1935–38		1923–26		1935–38	
Adenomatous goiter with hyperthyroidism	1,131	750	Diabetes	23	2.0	42	5.6
Exophthalmic goiter Adenomatous goiter with hyperthyroidism and exophthalmic goiter	2,340	1,132	Diabetes	15	0.6	19	1.7
Total	3,471	1,882	Diabetes	38	1.1	61	3.3
Adenomatous goiter without hyperthyroidism		2,277	Diabetes			38	1.67

* The patients entering the clinic because of recurrence of hyperthyroidism within the three-year period were counted more than once. The number of these patients, however, is too small to affect the significance of the data.

The question whether hyperthyroidism provokes the development of diabetes in predisposed patients may thus be answered in the affirmative by these statistics on diabetes with hyperthyroidism, at least in cases of adenomatous goiter with hyperthyroidism; the figures for exophthalmic goiter are inconclusive. Other information bearing on this question might be secured from study of the priority in appearance of hyperthyroidism in cases in which hyperthyroidism and diabetes are associated, but unfortunately the date of onset is difficult to determine for both diseases and conclusions based on such estimates appear valueless. In nineteen cases of diabetes and exophthalmic goiter in the series reported by Regan and me the hyperthyroidism apparently preceded the diabetes in ten, or 52 per cent, and in forty-two cases of diabetes

and adenomatous goiter with hyperthyroidism in this series the hyperthyroidism apparently came first in twenty-six, or 62 per cent (Table 6).

TABLE 6

PRIORITY IN APPEARANCE OF HYPERTHYROIDISM OR DIABETES IN 152 THYROID DIABETICS*

Condition.	Cases.	Hyperthyroidism preceding Diabetes.	
		Cases.	Per cent.
Primary hyperthyroidism (exophthalmic goiter)			
Fitz	22	21	93 5
Wilder	12	9	75 0
Joslin-Lahey	28	23	82 1
Total	62	53	85.5
Regan-Wilder	19	10	52 6
Secondary hyperthyroidism (adenomatous goiter with hyperthyroidism)			
Wilder	19	9	47 4
Joslin-Lahey	8	5	62 5
Total	27	14	51 9
Regan-Wilder	42	26	62 0

* Modified from Joslin, Treatment of Diabetes Mellitus, 6th ed., p. 574

The incidence of diabetes as a complication of adenomatous goiter without hyperthyroidism was studied only for the period 1935 to 1937. In these years it was 1.67 per cent (among 2,277 cases of adenomatous goiter without hyperthyroidism, diabetes was a complication in thirty-eight cases) This frequency is slightly less than that for diabetes in all new patients who registered at The Mayo Clinic for the year 1937, therefore, it probably is without significance. So far as has been determined, the presence of a nontoxic goiter is without influence on the course of diabetes or the effectiveness of insulin. However, at the clinic we have encountered temporary resistance to the action of insulin in such cases immediately after thyroidectomy, as is illustrated by the following report of a case:

A man fifty four years of age presented himself for examination with no other complaint than that of fatigue, which had been present for about two years Polyuria and polydipsia had been noted for several weeks but the urine had not been examined for sugar. The maximal weight of 250 pounds (113.4 kg) had been reached eleven years previously, and partly because of

quent experience has fully confirmed the validity of these conclusions.

A number of cases could be cited to illustrate how pre-existing diabetes is intensified by the occurrence of hyperthyroidism. The date of onset in hyperthyroidism is often difficult to determine. The same is true of diabetes. In the following case, previously reported (Wilder, December, 1926) it is reasonably certain that diabetes had existed for at least two years while hyperthyroidism had not been present for more than six months.

The patient was a woman, aged fifty nine years Marked polyuria and polydipsia developed in February, 1922 Sugar was found in the urine, but this was readily controlled by a diet until, in August, 1923, symptoms suggestive of hyperthyroidism were noted for the first time These were nervousness, intolerance to heat, increased perspiration and tachycardia Thereafter dieting proved ineffectual, and at the time of her admission to the hospital, February 16, 1924, the urine contained an abundance of sugar and the blood contained 0 252 gm of sugar for each 100 c.c. On a diet with a dextrose equivalent of 140 gm., an average of 50 gm. of sugar appeared in the urine daily. The basal metabolic rates ranged from +52 to +66 per cent. Later, glycosuria was controlled with 40 units of insulin daily, and on March 5 thyroidectomy was performed Thyroid tissue weighing 372 gm. was removed; this showed multiple adenomas The convalescence was uneventful; the basal metabolic rate fell, and by March 26 the same diet which previously required 40 units of insulin could be taken without insulin.

In this case a mild diabetes was made rather severe by the development of hyperthyroidism and resumed its mild state after the control of the latter by thyroidectomy.

Hyperthyroidism, as is well known, is wont to show alternating periods of exacerbation and remission. This is true both in that accompanying adenomatous goiter and in cases of exophthalmic goiter, although it is much more common in the latter. Exacerbations may occur spontaneously and these at times assume the intense form of the hyperthyroid crisis When diabetes coexists, any exacerbation is associated with intensified glycosuria and this may be so extreme that not enough sugar is burned to prevent ketosis. Under such circumstances acetone formation goes on apace, and serious acidosis and coma may result. In a case already reported in detail (see p. 247), there is good reason to believe that the three attacks of diabetic acidosis were precipitated in this manner.

The decreased efficiency of insulin in diabetes complicated

diet had been reduced to 205 pounds (93 kg.). In the last year an additional nine pounds (4 1 kg) had been lost.

Examination showed a man weighing 196 pounds (89 kg) with a blood pressure of 154 mm of mercury systolic and 100 mm. diastolic, and a pulse rate of 96. The thyroid gland, which was enlarged bilaterally, measured 6 by 10 cm and was very hard Examination of the urine revealed the presence of a reducing substance, and the value for the fasting blood sugar was 0 226 gm. per 100 c c. The basal metabolic rate was +4 per cent (two tests)

A diet containing 238 gm. of carbohydrate was prescribed. Compound solution of iodine (Lugol's solution) also was given. It was found necessary to use 25 units of insulin daily to control glycosuria. After ten days, the value for the fasting blood sugar was 0 161 gm per 100 c.c. and operation was performed Intense glycosuria followed and for the next seven days it was controlled with difficulty. The daily doses of insulin were 95 units, 115 units, 60 units, 70 units, 55 units, 55 units and 80 units respectively, and the amounts of sugar in the urine for the first four of these days were 17, 29, 12 and 30 gm respectively. The specimens of urine also all contained acetone and diacetic acid. The degree of postoperative reaction otherwise seemed not abnormal The maximal temperature, which was reached on the third day, was 102° F, and after the fourth day the patient was free from fever. Subsequently the doses of insulin could be decreased rapidly, so that by the end of the second week 12 units of protamine-zinc insulin in one dose daily was sufficient to prevent glycosuria.

The postoperative behavior of this patient was cause for some apprehension. There was little clinical evidence of hyperthyroidism preoperatively, and examination of the tissue revealed nothing to suggest it; nevertheless, the reaction postoperatively was like that of a mild thyroid storm, and as a result, the intensity of the accompanying diabetes was greatly augmented.

EFFECT OF HYPERTHYROIDISM ON DIABETES

In a preliminary report based on a detailed study of the metabolism in four cases, Boothby and I emphasized the clinical importance of recognizing exophthalmic goiter in cases of diabetes and pointed out that hyperthyroidism not only reduced the ability of the diabetic patient to utilize carbohydrate but decreased the efficiency of the unit of insulin and thereby increased the danger of sudden onset of diabetic coma. We also showed that the control of the syndrome of exophthalmic goiter by the administration of iodine, in cases in which diabetes was complicated by exophthalmic goiter, markedly improved the tolerance for carbohydrate and reduced the requirement for insulin. Subse-

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by hyperthyroidism has also been demonstrated by clinical experiments. In the case reported on page 247 twelve days after the second admission of the patient with diabetes and exophthalmic goiter the administration of iodine was discontinued. In the meantime, the basal metabolic rate had decreased from +47 to +20 per cent. The diet was constant at 2100 calories; its glucose equivalent was 140 gm., and on this regimen, with a daily dose of 90 units of insulin, the urine was free from sugar and acetone. The dose of insulin was held at 90 units daily, but after no more iodine was given the basal metabolic rate rose gradually and fourteen days later reached +48 per cent; simultaneously, sugar reappeared in the urine and increased in amount from day to day. The condition of the patient became distinctly worse, acetone appeared, together with symptoms of acidosis, and the carbon dioxide combining power of the plasma fell to 30 volumes per cent. The daily doses of iodine then were resumed; the basal metabolic rate declined and ultimately the daily requirement for insulin was lowered to 40 units.

Another influence of hyperthyroidism in many patients, with or without diabetes, is to deplete the liver of its glycogen The effect of this is twofold. first, it increases the sensitiveness of the organ to poisoning; second, it deprives the patient of the most important part of the mechanism whereby the body protects itself from hypoglycemia. In consequence, insulin reactions encountered in patients with diabetes and hyperthyroidism are likely to be severe. However, the sensitivity of these patients is to overdosage with insulin rather than to insulin *per se*. They suffer a lack of ability to correct hypoglycemia, not as has been inferred from the animal experiments of Burn and Marks,[6] any diminished requirement for insulin. On the contrary, the clinical evidence is clear that hyperthyroidism increases insulin requirement.

TREATMENT OF HYPERTHYROIDISM COMPLICATING DIABETES

In cases in which diabetes is complicated by exophthalmic goiter, the benefit derived from the administration of iodine is

striking. The basal metabolic rate is lowered, and as it falls tolerance for carbohydrate improves and the requirement for insulin is diminished.[7] When the complicating hyperthyroidism is that of adenomatous goiter, the effect of iodine is less pronounced or may be absent, but since it is not always possible preoperatively to exclude exophthalmic goiter in cases of hyperthyroidism, and since iodine can do no harm in such a case during the short period while the patient is being prepared for operation, it has seemed best to use iodine routinely, as a preoperative measure, when the basal metabolic rate is elevated.

Compound solution of iodine (Lugol's solution) is the preparation of iodine commonly employed The customary dose is 10 minims (0.6 c c. three times daily). If the patient is in acidosis, or for other reasons is unable to receive medicines by mouth, sodium iodide or even compound solution of iodine (Lugol's solution) may safely be injected intravenously with solutions of sodium chloride.

Thyroidectomy is clearly indicated in the large majority of cases of diabetes with hyperthyroidism. This is shown clearly by a complete follow-up study made in 1939 of all the thirty-eight cases of diabetes with hyperthyroidism reported by me in 1926 Twelve of the fifteen patients with exophthalmic goiter and diabetes were operated on. Seven of these had survived thyroidectomy an average of 13.8 years. The average duration of life in the five fatal cases was 8 1 years after thyroidectomy Death in these cases was attributed to coma, diabetes, lobar pneumonia, coronary thrombosis and heat stroke Two of the three patients who were not operated on died of coma and the other of diabetes seven months after dismissal. Twenty-one of the twenty-three patients with adenomatous goiter with hyperthyroidism and diabetes were operated on Five of these had survived thyroidectomy an average of 13 6 years The average duration of life in the sixteen fatal cases was 7 4 years after thyroidectomy. The causes of death were heart disease, seven; pneumonia, three, and

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required insulin postoperatively in doses much larger than those required by any of them preoperatively. The doses given postoperatively ranged from 15 to 120 units. The reactions also have been encountered postoperatively in cases of colloid goiter.

Operation in all cases of hyperthyroidism should be deferred until a maximal effect has been obtained from the administration of iodine and until the diabetes is under good control. The hepatic function should be studied, and if found diminished, the patient should be given a diet rich in carbohydrate and supplemented with vitamin A and a concentrate of the vitamin B complex for two or three weeks. In general, the diet of diabetic patients with hyperthyroidism should be higher in carbohydrate than otherwise is necessary, with due attention paid to the increased requirement for calories and vitamins To check glycosuria it sometimes is necessary to give insulin at short intervals—every two or three hours This particularly will be necessary if a thyroid storm follows the operation Protamine-zinc insulin may be used, but the rapidly changing requirement for insulin in these cases makes it impossible to depend on an insulin with retarded activity for more than a small fraction of the total insulin requirement In severe cases a close watch must be maintained preoperatively, and always postoperatively, to avoid acidosis on the one hand and hypoglycemia on the other. The peculiar sensitivity to the latter of patients with diabetes complicated by hyperthyroidism has been mentioned (see p. 254) Because of this sensitivity complete suppression of glycosuria should be avoided. In severe cases, if a thyroid reaction occurs preoperatively or after operation, large doses of compound solution of iodine (Lugol's solution) are indicated—up to 1 c c. every six hours—and when food is not retained dextrose and sodium chloride must be given intravenously. In such cases it also is advisable to add thiamin chloride to the solution for injection

PROGNOSIS IN DIABETES COMPLICATED BY THYROIDECTOMY

In adenoma with hyperthyroidism recurrence after thyroidectomy is very unusual, in exophthalmic goiter the incidence of recurrence is relatively high. In forty-two cases of adenomatous goiter with hyperthyroidism, no recurrence of hyperthyroidism

coma, gangrene—right leg, carbuncle on back of neck, cerebral hemorrhage, recurrent carcinoma, and acute cholecystitis, one each. One of the two patients not operated on died of cardiac decompensation three months after admission. The other died ten years later of cardiac and renal disease.

Joslin has reported the average duration of life subsequent to the onset of diabetes among deceased ex-patients in the early Banting (1922–1926), middle Banting (1926–1930) and later Banting (1930–1935) periods for all ages as 7.6, 8.4 and 11.0 years respectively. Considering all the patients in my series of 1926, except the five who did not have thyroidectomy, the average duration of life subsequent to the onset of diabetes was 12.4 years Considering only those patients who now are dead and again excluding the five who did not have thyroidectomy, the average duration of life subsequent to the onset of diabetes was 10 8 years The numbers in both of these groups are too small to justify comparison with the large groups (514, 897 and 981 cases respectively) of Joslin's deceased patients with diabetes studied by the Statistical Bureau of the Metropolitan Life Insurance Company. They, nevertheless, support the assumption that patients with hyperthyroidism and diabetes who receive satisfactory surgical treatment for their hyperthyroidism do as well as patients with diabetes free of this complication. The fact that four of the five who were not operated on died within a few months of the time they were dismissed from the clinic also carries significance.

Thyroidectomy is recommended for adenomatous goiter without hyperthyroidism as well as for hyperthyroidism, if adenomas are palpable and a centimeter or more in diameter, for the reason that such goiters frequently become toxic later and by their removal the patient is protected from danger of subsequent hyperthyroidism. The operation may provoke a temporary thyroid storm, not only if the goiter is already toxic, but even as has been illustrated (see p. 251) in cases in which the goiters clinically have been regarded as nontoxic, probably because of liberation of thyroglobulin by the operation and the absorption of this from the operative incision The fourth day after operation is the time of greatest reaction. In seven cases in which operation was performed for adenomatous goiter without hyperthyroidism, only four patients needed insulin before operation, yet six patients

required insulin postoperatively in doses much lar
required by any of them preoperatively. The dos
operatively ranged from 15 to 120 units. The react
been encountered postoperatively in cases of colloid g

Operation in all cases of hyperthyroidism should
until a maximal effect has been obtained from the ad
of iodine and until the diabetes is under good con
hepatic function should be studied, and if found
the patient should be given a diet rich in carbohydrat
plemented with vitamin A and a concentrate of the
complex for two or three weeks. In general, the diet o
patients with hyperthyroidism should be higher in carb
than otherwise is necessary, with due attention paid to
creased requirement for calories and vitamins. To chec
suria it sometimes is necessary to give insulin at short int
every two or three hours This particularly will be ne
if a thyroid storm follows the operation. Protamine-zinc i
may be used, but the rapidly changing requirement for i
in these cases makes it impossible to depend on an insulin
retarded activity for more than a small fraction of the total in
requirement. In severe cases a close watch must be mainta
preoperatively, and always postoperatively, to avoid acidosis
the one hand and hypoglycemia on the other The pecu
sensitivity to the latter of patients with diabetes complicated
hyperthyroidism has been mentioned (see p 254). Because
this sensitivity complete suppression of glycosuria should b
avoided. In severe cases, if a thyroid reaction occurs preopera
tively or after operation, large doses of compound solution o
iodine (Lugol's solution) are indicated—up to 1 c.c. every six
hours—and when food is not retained dextrose and sodium
chloride must be given intravenously. In such cases it also is
advisable to add thiamin chloride to the solution for injection

PROGNOSIS IN DIABETES COMPLICATED BY THYROIDECTOMY

In adenoma with hyperthyroidism recurrence after thyroid-
ectomy is very unusual, in exophthalmic goiter the incidence of
recurrence is relatively high. In forty-two cases of adenomatous
goiter with hyperthyroidism, no recurrence of hyperthyroidism

was seen. Of eighteen cases of exophthalmic goiter with diabetes seen in 1935, 1936 and 1937, seven were cases of recurrence operations having been performed at the clinic or elsewhere from one to ten years previously. Therefore, when the histologic examination of the tissue removed at operation shows the presence of regions of cellular hypertrophy and hyperplasia (indicative of exophthalmic goiter), the patient should be cautioned to watch for symptoms of recurrence, and upon their appearance, or if an otherwise unexplained increase occurs in his requirement for insulin, to resume the use of compound solution of iodine at once and report to his physician. Recurrence frequently can be controlled with iodine; if it fails, further resection of the thyroid gland is indicated.

Diabetes occasionally is arrested by thyroidectomy; in most cases in which it has been complicated by hyperthyroidism its intensity has been decreased. This is illustrated in a number of case reports by Buchanan, Holst, O'Day and Rohdenburg, but in none of these reports, so far as I can find, was the blood sugar determined after dextrose test meals, and without such examinations it is scarcely legitimate to claim, as some authors have done, that an actual cure has followed the removal of the thyroid gland. Holst reported observations on several instances of persistent glycosuria, in two of which dextrose test meals failed to cause glycosuria after recovery from thyroidectomy.

MYXEDEMA AND DIABETES

Some of the reputed recoveries of normal tolerance after thyroidectomy may be due to the development of a state of myxedema, such as occurs occasionally when exophthalmic goiter is complicated by thyroiditis. In a case reported by Holst, diabetes was manifested six months after thyroidectomy had been performed for exophthalmic goiter, during a recurrence. Two and a half years later myxedema appeared spontaneously and then a test meal of 100 gm of dextrose provoked no alimentary glycosuria. Several instances of spontaneous myxedema developing in the course of diabetes and resulting, as in Holst's case, in great amelioration of the tolerance, are to be found in the literature. A most interesting example previously reported from our clinic was the following:

A male child, aged seven years, had been a full-term infant with normal health and normal growth up to the age of fifteen months He then had manifested polydipsia and polyuria, and sugar had been found in the urine. He had been placed on a very strict diet, which, after six months, could be somewhat relaxed without causing a return of glycosuria. Delayed growth and increasing coarseness of the hair had led to the diagnosis of hypothyroidism when he was three years of age Thyroid treatment had been begun, but had been discontinued because of the return of intense glycosuria and the occurrence of acidosis During the period of thyroid treatment growth had been resumed; after its discontinuance growth again had stopped and the tolerance had improved so much that the child "could eat anything without excreting sugar."

At our examination at the clinic this patient presented a fully developed picture of juvenile myxedema—the face was dull and expressionless, the skin was dry and thick and the hair was coarse and scanty Mentality and phys- [illegible]

[illegible]

olism was raised very gradually The basal metabolic rate finally reached —10 per cent and at this time sugar appeared in the urine. Sugar continued to be excreted in amounts as high as 20 gm a day, and the value for the fasting blood sugar level reached 0.145 gm. per 100 c c A later report stated that the child was gaining in weight and strength, but showing sugar despite a rigid diet and administration of insulin.[4]

[illegible]

oxidation is proceeding at a relatively rapid rate a catalyst, such as insulin, undergoes a more rapid decay, whereas its life is longer and its efficiency consequently greater when all oxidations are taking place more slowly.

Mention has been made of an attempt to treat uncomplicated diabetes by [illegible]

[illegible]

reason that the patient was displeased at finding myxedema to be a more disagreeable disease than diabetes I should like to emphasize, especially to colleagues in physiology, that the effect of thyroidectomy in this case, on diabetes which previously had been as severe as that which follows total pancreatectomy in dogs, was every

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bit as effective in curing the diabetes, as hypophysectomy is reputed to be in de pancreatized dogs I even suggest that if a Houssay dog (hypophysectomized and pancreatectomized and not requiring insulin) could compare notes with a Banting dog (pancreatectomized and receiving insulin) he too probably would be dissatisfied

The results of thyroidectomy on thirty depancreatized animals (mostly dogs) collected from the literature by Dohan and Lukens were variable In almost half of these animals the results were interpreted by the original authors as indicating no effect, while in the remaining animals a decrease in the severity of the diabetic manifestations occurred. Dohan and Lukens, with six cats thyroidectomized four to thirty-four days before pancreatectomy, found, as compared to sixteen depancreatized cats, diminution of dextrose and nitrogen excretion of more than 20 per cent; with thirteen cats, thyroidectomized and depancreatized simultaneously, they found a less significant decrease in dextrose, nitrogen and acetone bodies *They* concluded, as Houssay had done, that the thyroid gland plays a relatively small part (compared to the hypophysis) in pancreatic diabetes The discrepancy between these observations on animals and clinical experience with thyroid de- differences in species

man, of complete
small fragment of
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CHAPTER XVI

DISEASES OF OTHER ENDOCRINE GLANDS COMPLICATING DIABETES

ACROMEGALY

The most striking manifestation of acromegaly, namely, the overgrowth of the acral parts of the skeleton, the flat bones of the head, pelvis and chest, and the soft parts of the hands, feet and face, is attributed to an excessive activity of the anterior lobe of the hypophysis. When the disease affects children it usually is spoken of as "gigantism," because in children union of the epiphysis is retarded (by suppression of development of sex hormones) and the period of sagittal growth is extended The characteristic abnormality of the acromegalic hypophysis consists of diffuse hyperplasia or adenoma of its anterior lobe, with unusual predominance of acidophilic cells

Incidence of diabetes in cases of acromegaly.—A relatively high frequency of association of glycosuria and acromegaly was commented on as early as 1884 by Loeb. It has been the subject of many subsequent reports but the published figures vary widely. The incidence of frank diabetes in cases of acromegaly observed at the clinic has not been as high as might be expected from many of the reports. Yater, who reviewed the records up to 1928, found only six instances of diabetes in seventy-nine cases of acromegaly. Subsequently, and up to September 14, 1938, among 139 additional cases of acromegaly, diabetes had been diagnosed in only fourteen. Adding the two series makes twenty instances of diabetes in 218 cases of acromegaly, an incidence of 9.2 per cent. Even this figure may be too high, because in case 4 of Yater's report, and in two cases of the later series, the diagnosis of acromegaly was doubtful, and in case 1 of Yater's report and in three cases of the later series, the diabetes amounted only to an alimentary glycosuria, which the high basal metabolic rates (from +30 to +63 per cent) alone might explain. If these cases in which the diagnosis was doubtful are excluded, it leaves only thirteen cases of frank diabetes for the entire series, representing

an incidence of only 6.0 per cent. In view of two other circumstances, namely that the thyroid glands in about half of the cases of acromegaly were adenomatous, and that in an indeterminable number of the cases of acromegaly associated with diabetes the diabetes clearly antedated the acromegaly, this incidence certainly is not impressive. It is very little higher, indeed, than that for adenomatous goiter with hyperthyroidism associated only with diabetes (see Chapter XV).

In many of these 218 cases of acromegaly the hyperpituitarism undoubtedly was burned out before the patient came to the clinic for examination, and glycosuria of sufficient intensity to be called diabetes might have existed in a previous more active stage of hyperpituitarism. It is questionable, however, whether a diabetes characterized by such impermanence deserves to be called diabetes mellitus. In other cases diabetes may have developed since examinations were made at the clinic, but the same could be expected in any group of nondiabetic patients, and particularly in a group of cases such as this, containing many cases in which the basal metabolic rate is elevated. In this connection it is important also to note that nonacromegalic tumors of the hypophysis may provoke glycosuria by pressure on or by invasion of the subthalamic region of the brain. Colwell and Logan, after only an incomplete survey, found thirty-eight cases in which nonacromegalic lesions of or near the hypophysis were accompanied by glycosuria or diabetes, and he suggested that this number compared favorably with the incidence of glycosuria and diabetes in cases of acromegaly.

Looked at the other way, namely, considering the incidence of acromegaly in cases of diabetes, the figures are as follows: For the period studied by Yater (to 1928) there were 4,160 individuals with diabetes, and of these only six had acromegaly, and in the later period (1928–1937 inclusive) there were 5,217 individuals with diabetes, and of these, only fourteen had acromegaly. If one accepts the diagnosis of diabetes in all of the twenty cases in which it was made, the incidence of acromegaly in cases of diabetes was 0.21 per cent, or about one case of acromegaly in 500 cases of diabetes.[1] The data imply that far too much emphasis

[1] This incidence is the same as that given by Davidoff for admissions of all patients with acromegaly to the Peter Bent Brigham Hospital, during the period when Cushing was chief of the surgical staff. In Joslin's series, according to Cog-

has been placed on the occurrence of diabetes in association with acromegaly, and constitute evidence that the hypophysis is not of such great importance in the production of clinical diabetes as has been supposed.

Effect of acromegaly on diabetes.—It is often stated that the diabetes of acromegaly runs an irregular course. However, Colwell and Logan studied the literature with this point in mind and collected reports of only seventeen cases in which an atypical course was claimed. In some of them dietetic control had not been maintained. Mild diabetes, whether associated with acromegaly or not, is likely to fluctuate widely in intensity, and in the cases of severe acromegalic diabetes that have come to our attention the symptoms and glycosuria have not responded to dietetic management in an unusual manner. Cushing's statement that the diabetes of acromegaly proves to be notably resistant to treatment with insulin also would not be justified by our experience. Notable insulin resistance has been conspicuously absent; for the most part the response to insulin has been rather normal and the insulin requirement not excessive. It is true, as is to be expected that more insulin is required in cases in which the basal metabolic rates are elevated than is required in other cases, and in such cases, as was illustrated by Yater, less insulin will be required if the basal metabolic rate can be depressed. In general, acromegaly is regarded as increasing the risk attending operations of all kinds, but the explanation for this is independent of any difficulty in handling the diabetes in cases in which acromegaly is complicated by diabetes. Yater, after reviewing the literature, concluded that the results of hypophysectomy in man had not satisfactorily demonstrated amelioration of coexisting diabetes by the operation. It is extremely difficult to remove all of the hypophysis, and in most reported cases the patients had not been observed with sufficient care after operation to permit conclusions.

PITUITARY BASOPHILISM AND DIABETES

Glycosuria was encountered in five of twelve cases of pituitary basophilism studied by Cushing. It apparently was mild in de-

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geshall and Root the incidence of acromegaly is about 1 in every 3000 cases of diabetes This lc [illegible]
at the neighborin [illegible]
patients referred [illegible]

gree, except in his case 11. In this case the patient previously had been examined by Woodyatt and Colwell, who reported to Cushing "a variable *glycosuria* and hyperglycemia, together with increased *nitrogen* excretion. On a diet with a daily glucose value of 201 gm., there was a daily excretion of 5 7 (?) gm of sugar (glucose), which was controlled by 50 units of insulin daily." Later, in Boston, when the diet was restricted but no insulin was given, the value for the fasting blood sugar was 0 214 gm. per 100 c.c. and a twenty-four hour specimen of urine contained 24.4 gm. of sugar and 29 2 gm of nitrogen. However, at a still later time, after roentgen therapy had been directed at the hypophysis and after the other symptoms had disappeared, the urine remained sugar free with an ordinary diet It would appear from this experience that glycosuria is more frequently an accompaniment of pituitary basophilism than of acromegaly, but that usually it is mild and, even when severe, it is transient, in the sense that the sugar disappears if and when the overfunction of the hypophysis can be corrected

HYPOPITUITARISM

Goetsch, Cushing and Jacobson called attention to an increased tolerance for carbohydrate (oral administration) in cases of clinical hypopituitarism Sansum and I, by giving dextrose intravenously at a constant rate in two cases of "Frohlich's syndrome," in which the patients had symptoms of hypopituitarism, found essentially the same limit of assimilation as in four normal controls. This suggested that the increased tolerance observed by those who used the oral method of administration might have been due to delayed absorption However, Goetsch, Cushing and Jacobson, in 1911, were able to demonstrate as Houssay later showed, that the intensity of pancreatic diabetes can be diminished significantly by hypophysectomy

In view of the animal experiments of Cushing, Houssay and others, the occurrence of clinical diabetes in cases of hypopituitarism should present something of a paradox, yet the association is by no means unusual. Gibson cited a typical case of hypopituitarism in which diabetes existed, and John reported on five cases with glycosuria, which represented 12 per cent of the cases of hypopituitarism observed at the Cleveland Clinic. Joslin also

cited an example. In his case the patient was twice in extreme acidosis

Infantilism.—In eight patients, four boys and four girls, from sixteen to twenty years of age reported by Gibson and Fowler, a syndrome of infantilism was encountered with proportionate dwarfism and severe diabetes. The authors presented evidence that hypofunction of the anterior lobe of the pituitary body was primarily responsible for the infantilism in these children, and commented on the disharmony between the association of this condition with diabetes mellitus. In their cases rather efficient management had been assured from the time the diabetes had first been recognized, but in other cases similar in all respects to theirs malnutrition undoubtedly has been primarily to blame. In some of the latter the malnutrition has been due to failure to use insulin; in others it has resulted from the prescribing of inadequate diets. In one tragic case the parents of a child, who was about six years old when he first was given a diet, failed to change the diet or again to consult a physician for ten years. In some of these cases normal physical and sexual maturity can be restored by effective treatment with adequate diets and properly adjusted doses of insulin; in others the resulting damage may be so serious (including probably secondary damage to the hypophysis and other glands of internal secretion) that restoration is impossible.[2]

HYPERADRENALISM

Paraganglioma.—Paraganglioma of the adrenal medulla gives rise to a syndrome characterized by paroxysmal attacks of hypertension. In these attacks the patient complains of nausea, cold extremities, headache, precordial constriction and faintness. The blood pressure in a case reported by Dr. Charles H. Mayo, although normal in the intervals, rose in attacks to 280 mm. of mercury systolic and 110 diastolic, and the capillaries of the nail folds would be completely obliterated. An excellent review of the subject is one by Donzelot, who in 1934 reviewed the eleven reported

[2] Houssay has suggested the possibility that defective pituitary secretion may be responsible for coincident dwarfism and diabetes, lack of growth hormone producing the former and lack of pancreatotropic hormone the latter. This sounds to me like begging the question both ways, furthermore, Anselmino and Hoffman's observations on pancreatotropic hormone, to which Houssay referred in this connection, have not been accepted by critical investigators

instances of the disease then in the literature. In a case which came to my attention two years later, Dr. Walters removed a tumor 10 5 cm. in diameter, and from half of this mass Dr. Kendall was able to isolate, in crystalline form, 120 mg of adrenalin. The well-known glycogenolytic action of adrenalin might lead one to expect glycosuria in this disease, but so far as I know this has not been observed. In the case reported by Kelly, Piper, Walters and me, the concentration of the blood sugar at the end of one attack was only 0.118 gm. per 100 c.c.; at another time, during an interval between attacks, it was 0 090 gm. per 100 c.c.

Lesions of the adrenal cortex.—In contrast to the apparent infrequency of glycosuria in cases of tumor of the adrenal medulla, glycosuria occurs not uncommonly in association with tumors and hyperplasia of the adrenal cortex. A review of the literature by Duncan and Fetter revealed eight proved cases of adrenocortical tumor with so-called diabetes, and Long made the statement that he and Lukens found evidence of "impairment of carbohydrate metabolism" in a half of fifty-five reported cases The experience at the clinic (1938) was studied with Kepler. It comprises eight cases of tumor (Table 10) and two of hyperplasia of the suprarenal cortex in which the diagnosis was proved by operation or necropsy.

Two of the patients with tumor in the report made with Kepler were girls. Their ages were twenty-three months and nine years respectively. The patients in the remainder of the cases were women. Frank diabetes was present in one of these cases and glycosuria associated with a value for blood sugar of 0 140 gm. per 100 c c. (three hours after breakfast) was present in another. Dextrose tolerance tests were made in four other cases and in two of them the responses were abnormal (Table 7). Urine containing from 4 to 6.5 per cent of sugar was excreted by the patient with frank diabetes and the fasting blood sugar value was 0 143 gm. per 100 c.c. Insulin, however, was not required for control The patient died shortly after the operative removal of the adrenocortical tumor and there were no other findings of significance at necropsy.

In all eight of these cases the adrenal tumors were removed One of the patients succumbed after operation, three died within a year as a result of recurrence or metastasis The remaining four

TABLE 7

Carbohydrate Metabolism in Cases of Adrenocortical Tumor

Age of patient.	Glycosuria.	Fasting value for blood sugar, gm. per 100 c c	Dextrose tolerance test, blood sugar, gm per 100 c c.				Comment.
			Fasting	½ hr	2 hr.	3 hr.	
23 mo	0	0 081					No dextrose tolerance test performed
9 years	0	0 068	0 068	0 118	0 119	0 116	
19 years	0	0 114	0 098	0 205	0 155	0 065	
25 years	—	0 082				0 140*	
35 years†	—	0 076	0 076	0 155	0 050	0 082	
33 years	0	0 075					No dextrose tolerance test performed
37 years	—	0 143					Clinical diabetes (see text)
39 years	0	0 073	0 078	0 205	0 242	0 093	

* Blood sugar determined three hours after breakfast.

† Glycosuria had been present prior to examination at clinic, and at that time the fasting value for blood sugar was 0 120 gm. per 100 c.c.

were alive one to five years after operation, all stigma of virilism having disappeared and complete health apparently being restored None of these patients, when last heard from, had diabetes, and although dextrose tolerance tests were not made the values for the fasting blood sugar, which were obtained elsewhere in two cases, were normal.

One of the patients in the two cases of adrenocortical hyperplasia was a woman, aged forty-six years, who presented frank evidence of adrenal virilism. She had, in addition, an intense alkalosis associated with hypochloremia (carbon dioxide combining power of the plasma 112 volumes per 100 c c., plasma chloride 425 to 520 mg. per 100 c c), and frank diabetes A twenty-four hour specimen of urine contained 47 0 gm. of dextrose and the fasting value for blood sugar was 0 236 gm per 100 c c. Sixty-five units of insulin were required to maintain the urine free of sugar, although the diet was low in carbohydrate. Roentgen therapy was applied to the pituitary body without benefit, and death occurred two months later. The terminal illness was characterized by periods of tetany, which could be controlled in part by injections of sodium chloride, also by a progressive anemia with a very marked reduction in the blood volume At necropsy both adrenal glands were found to be markedly enlarged (combined weight 49 gm) as a result of a high degree of cortical hyperplasia. A thymic tumor, 5 cm in diameter, was present, and there was a small abscess at the head of the pancreas which communicated through several tracts with the duodenum The tail of the pancreas was normal The changes described by Crooke were present in the basophilic cells of the pituitary body, but no basophilic adenomas were found, although serial sections were made

to control glycosuria The left adrenal gland was explored surgically and a tumor, which was thought to be a carcinoma (measuring 2 5 by 5 by 1 cm) was removed without benefit Glycosuria in this case later became exceedingly difficult to control because of insulin reactions, and the daily dose of insulin eventually was reduced to 10 units The patient died at home about six weeks after the operation, and necropsy (performed there) showed the liver to be almost completely replaced by tumor tissue and the portal vein to be almost completely obstructed The lesser omental cavity was filled with involved lymph nodes The head of the pancreas was replaced by tumor tissue, but the last 5 to 8 cm of the tail of the pancreas was not involved The adrenal gland on the right side was almost identical in size, color and histologic appearance to that on the left, which had been removed at operation Sections were examined by several pathologists; the reports were conflicting, however, both adrenal cortices were extensively hyperplastic, and apparently the carcinoma arose independently from the head of the pancreas There is no reasonable doubt that the symptoms of virilism in this case were the result of the hyperplasia of the adrenal glands Because of the normal appearance of the tail of the pancreas it is unlikely that the carcinomatous involvement of the head of the pancreas in itself was responsible for the diabetes The terminal hypoglycemia may have been the result of hepatic insufficiency.

ADDISON'S DISEASE

That the value for the blood sugar is low in Addison's disease has long been known. It was commented on by Porges in 1910 Diabetes thus would not be expected in this disease, and so far as I am informed it has not been observed.

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CHAPTER XVII

COMPLICATING DISORDERS OF THE EYES IN DIABETES

The ocular complications of diabetes are a cause of increasing concern. In more than 2000 cases of diabetes observed by Waite and Beetham the incidence of the more important ocular complications was as follows: wrinkles of the posterior cornea, 26 per cent; weakness of accommodation, 21 per cent; retinitis, 18 per cent; cataracts (all), 6 5 per cent, and "flocculi cataract" of juvenile diabetes, 0 5 per cent.

WRINKLES OF THE CORNEA

The frequency of arcus of the cornea was no greater in the diabetic than in the nondiabetic eyes studied by Waite and Beetham, but a striking difference was found in the occurrence of wrinkling of Descemet's membrane as determined by examination with the slit-lamp and corneal microscope This abnormality was present in 26 per cent of the diabetics and in only 10 5 per cent of 914 eyes of nondiabetics It seemed not to be correlated with the blood sugar level, the dose of insulin or the intra-orbital pressure, but frequently was associated with arteriosclerosis and retinitis. It occurred in 60 per cent of patients with gangrene and in 51 per cent of those with deep retinal hemorrhages The lesion is of relatively minor significance, causing little if any disturbance of vision.

WEAKNESS OF ACCOMMODATION AND TRANSITORY REFRACTIVE CHANGES

The transitory visual disturbances so frequently encountered when patients with uncontrolled diabetes are first treated have been considered under "Insulin presbyopia" (see p. 98). Similar loss of power of accommodation is observed by patients at the onset of their disease, if the onset is acute The degree of the disturbance depends on the age of the patient; it is slight in youth and greater as the age of normal presbyopia is approached

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The difficulty, as I previously mentioned, seems to reside in a loss of elasticity of the lens, which in turn probably is dependent on shifts of osmotic conditions. Another explanation, suggested by Waite and Beetham, is that excessive deposits of glycogen in the pigment epithelium of the ciliary bodies hampers the movement of the intrinsic muscles. The frequency of occurrence is probably greater than that indicated by the figure 21 per cent given by Waite and Beetham. I suggest that the disturbance depends entirely on rapidly developing or rapidly receding intensity of diabetic abnormalities, and that if looked for at the right time it would be found in some degree in 100 per cent of all cases of intense diabetes.

RETINAL LESIONS

Occasional medical writers have objected to the term "retinitis" as used to designate the lesions of the fundus of the eye characteristic of diabetes, preferring to call the condition "retinosis or retinomalacia," on the score of its not being inflammatory. I am inclined, however, to agree with Barkan and Gray that there is no good reason, since the pathogenesis is not yet settled, for discontinuing to use the familiar term "diabetic retinitis."

Diabetic retinitis.—The retinitis of some patients with diabetes who suffer also from hypertension may depend entirely on the latter disease. Constriction and sclerosis of the arterioles with superficial cotton-wool patches and hemorrhages with or without edema are seen. This picture differs in no way from that encountered in severe hypertensive disease not associated with diabetes.[1] Wagener, Dry and I found such a lesion in 1.1 per cent of 1,052 consecutive cases of diabetes In an additional 16.6 per cent of these cases, however, in which hypertension was or was not present, the retinal lesions encountered were of a type which is so characteristic of diabetes that experienced observers frequently are able to recognize the existence of diabetes from the appearance of the eye grounds alone. In many cases the lesion

[1] Much of what follows in this discussion of retinitis is reproduced from a paper published jointly by Wag[illegible] review of 1052 consecutive cases of diabetes [illegible] an ophthalmologist—in almost all [illegible] his lesion extends back to a study [illegible]

characteristic of diabetes is superimposed on that attributable to hypertension.

The lesion of the retina characteristic of diabetes seems to progress through successive phases in the development of some common underlying disturbance. The earliest and mildest phase is attended with the appearance of tiny punctate hemorrhages situated usually in the vicinity of dilated terminal vessels in the region of the macula. These hemorrhages are deep in the retina; therefore, they are almost always round. At a later but still early stage in the development of the retinal disease a few shiny punctate exudates are seen, which also apparently lie in the deeper layers of the retina, above or below the macula. These exudates almost always are in association with the round hemorrhages described [2] At this stage the picture is typical of what Hirschberg called "central punctate retinitis." However, as the lesion progresses similar exudates and hemorrhages appear in any part of the retina; the exudates coalesce and in the macular region may fuse into large necrotic-looking plaques that seriously interfere with vision; larger hemorrhages of irregular form also are seen.

In some cases, in which the general picture is the same as that described, more edematous and superficially situated exudates are seen. At times these are identical in appearance with the cotton-wool patches of hypertensive retinitis, and like them lie in the nerve fiber layer of the retina; in many cases they probably are dependent on a complicating hypertension with angiospasm, but in others, in which they are more deeply situated, more yellowish in color and more chronic in appearance than the cotton-wool patch typical of hypertension, they may be independent of hypertensive disease.

In these varieties of retinal lesions (the punctate hemorrhagic lesion, the lesion consisting of hemorrhages with punctate exudates, and the lesion consisting of hemorrhages with both punctate and cotton-wool like exudates) the arteries usually appear normal or at most give evidence of a moderate degree of sclerosis. On the other hand, the veins usually are mildly dilated. In a certain number of cases marked abnormality is observed in the veins;

[2] Waite and Beetham described waxy exudates as occurring independently In our experience hemorrhages almost always accompany these, and in the mildest form of the lesion occur without them

this is different apparently from that seen in any other disease, although resembling somewhat the lesion of the retina produced by tuberculosis and syphilis. The veins are dilated; in some the dilatation is nodular with intervening constrictions suggestive of the presence of thrombi. Segments of a vein may be ensheathed in a layer of heavy grayish-yellow exudate and other segments may be obliterated Unusually large hemorrhages are also found with this marked disease of the veins and rather commonly hemorrhages occur into the vitreous. As a result of, or as a sequel to, the latter, bands of scar tissue form and new vessels proliferate into the vitreous, giving rise to a picture of retinitis proliferans which resembles that described in tuberculosis and syphilis. Contraction of the bands of scar tissue may cause detachment of the retina. This is the most serious type of retinitis found with diabetes. It always arouses a suspicion of retinal tuberculosis, but since all transitional stages can be observed from the typical retinitis described by Hirschberg, through the stage of mild abnormalities of the veins to the terminal picture of retinitis proliferans, among patients who give no other evidence of syphilis or tuberculosis, the severe lesion in question seems to be the terminal stage of a pathologic condition primarily of diabetic origin.

In the study made with Wagener and Dry hemorrhagic lesions of the retina, characteristic of so-called diabetic retinitis, were found, as stated, in 175, or 16.6 per cent, of the 1,052 consecutive cases of diabetes. In fifty-eight of these 175 cases the lesion consisted of deep hemorrhages alone, in another eighty-eight cases exudates were present, and in the remaining twenty-nine gross disease of the veins existed with or without proliferation. The lesions occurred predominantly among patients who were more than forty years of age and in cases in which the diabetes was complicated by hypertension, arteriosclerosis or nephritis, but in twenty-three cases no other evidence of vascular disease except the retinal hemorrhages could be found. In the absence of other vascular disease, the retinitis usually was mild and consisted of deep round hemorrhages alone or of hemorrhages with small deep exudates, but the existence of such cases suggests the primary dependence of diabetic retinitis on some diabetic abnormality of metabolism. However, there was no correlation between the occurrence of

intensity of retinitis and the severity of the diabetes or the effectiveness of its control, either in the series of cases studied by Waite and Beetham or in our series The only evident correlation was with the duration of the diabetes In our series, sixty-six of the patients who had retinitis were examined two or more times over successive years, and progression of the lesion was noted in thirty-seven.

Satisfactory treatment for diabetic retinitis is yet to be found. The lesions in question seem not to be affected favorably or unfavorably by the use of insulin or by the degree of control of the concentration of the blood sugar However, I recently have entertained the suspicion that attacks of hypoglycemia from overdoses of insulin may provoke hemorrhage of retinal vessels, just as they are known to be followed by multiple hemorrhages of the brain. The coagulation factors of the blood and the fragility of the capillaries of the skin have not been abnormal; nevertheless, the nature of the lesion is suggestive of some type of hemorrhagic disturbance, possibly dependent on a structural abnormality of the retinal veins In consequence, we have resorted to treatment with moccasin venom, as described by Watkins, which has been shown to be of benefit in other hemorrhagic conditions. The results of this treatment have been encouraging In other cases we have given large (200 mg.) daily doses of ascorbic acid, together with several ounces of lemon juice. In cases in which there was much exudation we also have administered potassium iodide [3]

Lipemia retinalis —In diabetic acidosis of long duration, and rarely otherwise, the fat content of the blood may rise to very high values—from 4 to 12 per cent, or more.[4] Under such circumstances the retina pales and the veins and arteries are salmon

[3] Mylius found normal blood pressure in fifteen of his fifty-nine cases of diabetic retinitis He also expressed the opinion that the essential abnormality in the production of hemorrhage and exudation is primarily a disease of the retinal veins Barkan and Gray suggested that the early pin-point, deep-seated hemor-

colored instead of red. They may even appear white. There is no close correlation between the appearance of the retina and the amount of fat in the blood; the former depends to some extent on the degree of dispersion of the fat. The explanation for the appearance of the vessels of the retina, according to Heine, is that the droplets of fat in the blood tend to accumulate close to the walls of the arteries and veins, leaving the erythrocytes in the axial stream. Diabetic xanthomatosis frequently is associated. The hopeless prognosis formerly attached to lipemia retinalis is no longer justified. Among the 108 cases of diabetic coma reported from my service by Baker, the condition was present in seven and in six of the seven cases the patients recovered. In ten cases reported by Root six of the patients were living or had survived the occurrence of the abnormality for many years. The prognosis from the standpoint of the eyes is good; with control of the acidosis the lipemia usually subsides within a few days, and the retina resumes a normal appearance.

CATARACT

The incidence of the common variety of senile cataract found by Waite and Beetham in their series of diabetic patients was 6 per cent; it was somewhat less than that for the nondiabetic patients examined. The experience in The Mayo Clinic, I believe, is similar. The diagnosis of cataract depends on an arbitrary decision as to what degree of lenticular opacity constitutes a cataract. Consequently, comparison of statistics obtained by different observers is impossible. In the year 1937 the diagnosis of cataract was made in only twenty-six (2.2 per cent) of the 1,184 cases of diabetes encountered at the clinic. Operation was performed in only fifteen of these. The senile cataract of diabetic patients differs in no way from that encountered among nondiabetic persons.[5]

[5] Carey and Hunt, analyzing thirteen cataractous lenses from diabetics, ten normal lenses, and thirty cataractous lenses from nondiabetic individuals found the phosphorus content of the cataractous lenses of the diabetics to be much lower than that of the normal lenses or cataractous lenses of nondiabetic persons. The average values were 6.2, 16.5 and 19.7 mg. per cent respectively. The calcium content of the diabetic and nondiabetic cataractous lenses was about the same, although about three times that of the normal lenses from normal persons. Whether the difference in phosphorus content and the correspondingly greater calcium-phosphorus ratio is significant of the cataract in the diabetic lens, or of the lens as such, is not clear, since normal lenses from diabetic individuals were not examined.

Another rare form of cataract which is peculiar to diabetes, which Duke-Elder has called "true diabetic cataract" and which Waite and Beetham referred to as "flocculi cataract," is characterized by rapidly developing subcapsular vacuolar degeneration of the lens It occurs among young people with severe diabetes and often is reversible with control of the diabetes. This true diabetic cataract is rare, even more so than is suggested by the figure 0 5 per cent given by Waite and Beetham. Using the slit-lamp and corneal microscope in their study, they presumably found many cases in which interference with vision was too little to attract attention otherwise. This type of lesion was encountered only six times by von Noorden in his enormous experience with diabetes (von Noorden and Isaac), and I can recall only a very few instances of it, all of them occurring in children or young adults. The case of a child eleven months of age reported by Major and Curran is that of the youngest patient on record.

If the occurrence of hypoglycemia (insulin reaction) is avoided during the period of postoperative convalescence, the operative treatment of cataract carries no greater risk in the presence of diabetes than usual. An insulin reaction, occurring before the wound of the iris has healed, may provoke bleeding into the anterior chamber or extrusion of the vitreous humor and detachment of the retina. Because of this danger, it is safer to treat these patients for a week after operation, without insulin, if this can be done, otherwise with only enough insulin to prevent gross glycosuria and acidosis. Hyperglycemia or moderate glycosuria does not delay the healing of the iris and sclera.

DEPIGMENTATION OF THE IRIS

Waite and Beetham, examining routinely without selection 4,001 eyes of diabetic patients in the New England Deaconess Hospital, found 258 or about 6 per cent with evidence of depigmentation of the iris In a series of 914 eyes of nondiabetics only 2 per cent were similarly affected. The abnormality has not been

The conclusion of Waite and Beetham that senile cataract is no more common in diabetic than in nondiabetic persons is opposed to certain other reports. Much

observed in patients treated at The Mayo Clinic with relatively high fat diets. That it may depend on a deficient intake of carriers of vitamin A (butter and cream) is suggested by the work of Ralli, Gresser and Flaum, who found that changes of this type developed in depancreatectomized dogs when the diet was low in vitamin A, but not otherwise.

AMBLYOPIA AND OPTIC ATROPHY

De Schweinitz and Fewell called attention to an unusual susceptibility of diabetics to tobacco amblyopia and Waite and Beetham, using tangent screen measurements, discovered such amblyopia in fourteen of their series of cases of diabetes. The defect starts as an enlargement of the normal blind spot, especially for green and red. As it progresses, it extends to the macula so that reading vision, which at first is unaffected, later is involved. It is thought that the toxic agents responsible "poison the retinal ganglion cells, rather than the fibers of the optic nerve itself." Carroll in particular has emphasized the importance of nutritional deficiency in producing tobacco and alcohol amblyopia. In seven of a series of eight cases improvement in vision was obtained by giving yeast and an adequate diet, although the patients continued to consume their customary amounts of alcohol and tobacco. The prognosis in amblyopia of this type is good if the patient will omit tobacco and alcohol, provided optic atrophy has not already set in. Free elimination by bowel, bladder and sweat glands, and the use of thiamin chloride as well as yeast are indicated. Sedatives may be given at first to tide the patient over a very difficult period. Unusually rapid recovery has been observed after administration of the pancreatic tissue extract, padutin (B. P. C.).

Wolfram and Wagener described the occurrence of simple optic atrophy in four diabetic siblings on our service. The patients were children, two boys and two girls with ages ranging from seven to fifteen years. There was no other family history of poor vision and, except for one paternal aunt, no family history of diabetes. The diabetes preceded the onset of noticeable loss of vision in three of the four children, but in the fourth the optic atrophy came first. The diets had been grossly deficient in vitamins, but four other children of the same family, presumably receiving similar food, had remained passably healthy.

CHAPTER XVIII

COMPLICATING DISORDERS OF THE NERVOUS SYSTEM IN DIABETES

The part played by the central nervous system in the homeostasis of the blood sugar and the provocation of hyperglycemia and glycosuria already has received consideration. When physicians first were informed of the important discoveries of Claude Bernard, the nervous disorders encountered in cases of diabetes were looked upon as causing diabetes; in later years the neuropathies most frequently associated have come to be recognized as results of the disease, if related at all, rather than causes.[1]

Every known neurologic disorder may be associated with diabetes: depression, dementia, chorea, parkinsonism, multiple sclerosis, hereditary ataxia, residues of encephalitis and poliomyelitis, epilepsy[2] and many others, but etiologic interdependence or relationship can only be recognized in a small number of conditions, and these in turn, for the most part, seem to depend more on the vascular accompaniments of diabetes than on any of the known disorders of metabolism in this disease. The neuropathies provoked by overdosage of insulin represent another subject and are considered separately.

[1] The significance in diabetes of neuroses and organic diseases of the nervous system, as well as the subject of so called neurogenous diabetes, was fully considered by von Noorden and Isaac. Their concluding remark deserves reiteration: "By and large, the injurious influence of diabetes on primary and secondary neuritises and other organic diseases of the nervous system is much greater and can be determined much more frequently than the reverse. Therefore, only under very unusual circumstances should one abandon the therapeutic principle: 'always consider the diabetes first.'"

[2] The suggestion has been made at times that diabetes provides immunity to epilepsy and asthma. Both of these conditions occur infrequently among diabetics, but Allan reported two cases of each in the 840 cases of diabetes registered in the clinic in 1930, and other cases of each have been encountered in other years. The occurrence of epilepsy was studied in the Joslin Diabetic Clinic of the Deaconess Hospital by Jordan (1933) who found nineteen cases with almost undoubted epilepsy among the records of 9,503 diabetic patients. This incidence appears small, but when it is remembered that epilepsy is predominantly a disease of youth, whereas diabetes for the most part affects individuals past fifty years of age, it probably is not unusual. Root (1937) cited König as finding an incidence for bronchial asthma in diabetic patients of 0.25 per cent.

The abnormalities of the nervous system which occur with sufficient frequency to be considered true complications of diabetes are affective disorders, encountered in cases of severe or moderately severe diabetes in which the patients are not under treatment, lesions of the peripheral nerves (nerve trunks and spinal cord), which give rise to the symptoms and signs commonly diagnosed as diabetic neuritis, and cerebrovascular accidents resulting from hemorrhage or thrombosis of sclerotic arteries.

AFFECTIVE DISORDERS

The mentality and emotional tone of patients with severe, uncontrolled diabetes frequently are disturbed In its milder form this complication manifests itself in psychic languor, loss of memory and will, depression and resistance to the suggestion that treatment will be helpful When present, it intensifies the objection to the use of insulin, which so frequently is encountered with new patients even when they possess their normal mental faculties. The disturbance adds greatly to the difficulty of imparting instruction; indeed, because of it instruction of the patient is best postponed until treatment has been instituted and the mentality has improved One then is frequently surprised to find that a man or woman who seemed to be stupid and stubborn has turned into an alert optimist, eager to learn and full of courage.

The usually rapid response of this disorder to the treatment of the diabetes establishes its dependence on the abnormal metabolism and disturbed osmotic relationships of the untreated disease Once they are corrected the normal psyche is restored, just as the removal of the responsible etiologic factor is followed by relief in toxic psychosis of other origin.

Much less common is a more severe psychosis characterized by intense melancholia and leading possibly to suicide. The older French writers on diabetes regarded the "délire de ruine" as characteristic of this diabetic insanity, "vésanie diabétique." The patients believe they have lost their fortunes and are faced with financial ruin. The condition certainly is extremely rare. Its occurrence usually is limited to middle-aged patients and its infrequency prompted von Noorden and Isaac to regard it as an

involutional psychosis and to consider its association with diabetes as coincidence.[5]

DIABETIC NEURITIS

The frequency with which peripheral pain, disturbance of reflexes and loss of the motor power of muscles are encountered in cases of diabetes at once establishes a relationship to diabetes of the disorders responsible for these disturbances. Woltman and I found peripheral pain recorded in the routine histories of 10 per cent of 2000 consecutive cases of diabetes In thirty-three cases anesthesia was recorded, in ninety-two paresthesia was present, and in an additional sixty-six the patients complained of numbness of the feet There also were ten trophic ulcers typical of the so-called mal perforant. Jordan (1936), in a much more intensive study of the neurologic symptoms of 461 patients examined in the Joslin unit of the New England Deaconess Hospital found that 45.3 per cent had diminished or absent patellar reflexes. He quoted Bouchard, who, in the year 1884, found the knee jerks absent in 28.5 per cent of cases of diabetes, as well as Severinghaus, who in 1931 recorded pain in 49 per cent and reduced reflexes in 57 3 per cent of diabetic patients especially examined for these abnormalities.

In addition to pain, changes in reflexes, anesthesia and paresthesia, the symptoms and signs encountered in diabetic neuritis are tenderness of nerves, paralysis of individual muscles, including the extrinsic and intrinsic muscles of the eyes and the muscles of the bladder and rectum. However, in contrast to many other forms of neuritis, the sensory disturbances predominate and paresis and paralysis are complained of infrequently. At least Woltman and I found the complaint of motor weakness recorded in only twenty-nine of the 2,000 diabetic histories we reviewed, and in this group of cases the muscles innervated by the peroneal

[5] Von Noorden and Isaac commented that the patients affected with this disorder are usually rich men, and cited three examples of the condition in each of which the patient, believing himself to be faced with financial ruin, had subjected his family to unaccusto[illegible] cases that might be classifiec[illegible] physician with relatively mild [illegible] cial reverse in connection wi[illegible] lucrative practice, the affecti[illegible] Controlling his diabetes was [illegible] prevent his death by suicide.

nerve were most frequently involved, leading to the foot drop of so-called crossed-leg paralysis described by Woltman.[4]

What constitutes diabetic neuritis? Woltman and I emphasized the importance of distinguishing between the pain frequently complained of by dehydrated patients of all ages in diabetic acidosis and the neurologic abnormalities encountered in cases in which the diabetes was under control. The former type of pain rapidly disappears on restoration of the balance of water and salt, the latter is affected only slowly, if at all, by the treatment of the diabetes. We also distinguished between the chronic neuritis, typical of treated diabetes, and the areflexia which was observed with great frequency among patients of all ages in the era before the discovery of insulin. Diabetic patients in those days often were cachectic and the areflexia of those who survived to benefit from insulin disappeared in many cases as the nutrition of the patients improved. The diabetic neuritis encountered today occurs for the most part among patients past fifty years of age and very rarely indeed among the very young who have received adequate treatment It is not related in severity to the intensity of the diabetes or the dose of insulin required for control, and it almost always is associated with extensive vascular disease.[5]

[4] Muscular paralysis or paresis was found in a larger percentage of the cases studied by Jordan (1936) and the group of muscles innervated by the peroneal nerve was involved in not more than half of them The quadriceps femoris muscle was affected in twenty-one cases, and in three there was weakness of some group of muscles of the arm Paresis of the external ocular muscles, not attributable to apoplexy, was noted in three cases reported by Root (1922, January, 1933) and in one reported by Jordan (1936), who quoted Collier as commenting on the frequency of this association

[5] For reasons that are not explained to my satisfaction, Jordan (1936) divided [illegible]

[illegible] and glycosuria were controlled Of the thirty-four cases placed by Jordan in this category, dehydration was present in ten and acidosis in nine. The remainder I [illegible]

Diabetic pseudotabes.—Occasionally various sensory and motor disturbances are so associated in the same case that the clinical picture bears some resemblance to tabes dorsalis.[*] A true Argyll Robertson pupil (fixed to light, reacting to distance, dilating only partially and in some cases even contracting on administration of mydriatics) was noted in five of Jordan's (1936) cases; more frequently the reaction is sluggish both to light and distance. Weakness of the bladder with urinary incontinence or retention or both also may occur and at least moderate trabeculation of the bladder was found in two of seven such cases studied by Jordan and Crabtree. Various names have been applied to this condition: polyneuritis diabetica, tabes diabetica and pseudotabes diabetica. Four cases with sufficiently disseminated abnormalities to justify the diagnosis were included in the 2,000 cases of diabetes I reviewed with Woltman. The essential features in one of these were as follows:

The patient, a farmer aged fifty-five years, had suffered from diabetes for fifteen years without adequate treatment. For one year he had had pain in his legs, numbness of the feet and epigastric pain associated with a feeling of fullness (distention pain). The pain in his legs was sharp and darting; usually it was most severe between 5 and 9 a.m. It was relieved rather than exacerbated by exercise and was aggravated by changes in the weather. The inner side of the thighs and the knees were hypersensitive, as was also the skin of the upper part of the abdomen. There was no history of venereal infection, the Wassermann test was performed several times with negative response, and the data obtained by spinal puncture were negative, except for a positive Nonne test. The blood pressure was 150 mm. of mercury systolic and 90 diastolic. Mild diabetic retinitis of the central punctate type was found and the T wave in lead I of the electrocardiogram was inverted. The urine contained 4.2 per cent of sugar, but no acetone. A value for the blood sugar was 0.280 gm. per 100 c.c. The pupillary reflexes were normal, but the tendon reflexes of the left upper extremity were diminished, the patellar reflexes were obtained only on reinforcement and those of the Achilles tendons were absent. The calves of the legs were tender to pressure, sensibility for touch, pain and temperature was slightly decreased over the feet, and sensibility to pain was delayed, also the vibratory sensibility at the malleoli was reduced. The nervous signs and symptoms were not affected by controlling the hyperglycemia, although sometime later temporary relief from the pain followed resort to an exclusive milk diet elsewhere. A year later the patient contracted erysipelas of the face and died.

Necropsy included examination of the spinal cord and peripheral nerves. The cord and nerve roots showed nothing that might be regarded as abnormal, considering the age of the patient. In the peripheral nerves, however, rather marked degeneration was found, associated with thickening of the walls of the nutrient arteries.

[*] An article by Major provides a complete discussion of this subject.

Pathologic anatomy.—The pathologic examination of the nerves in this and nine other cases of diabetes led Woltman and me to conclude that the most significant lesions in diabetic neuritis are in the nerve trunks, that these consist of patchy areas of degeneration, more marked distally and associated with thickening of the walls of the nutrient vessels, and therefore, that arteriosclerosis of the nutrient vessels of the nerves, and the ischemia resulting therefrom, probably play a leading part in the production of diabetic neuritis.

Pryce and Rimbaud also have been impressed by the importance of arteriosclerosis in diabetic neuritis, and Jordan, Randall and Bloor were led to support this view. The chemical studies by the latter of the lipid constituents of nerves yielded information of great interest. The findings in brief were that the phospholipid, cholesterol and cerebroside values in the nerves of diabetics were significantly smaller than the average values obtained in nerves of normal persons, that the values were lower among diabetic patients with areflexia than for those with normal reflexes, lower in distal nerves than in proximal nerves and progressively lower the more marked the associated vascular disease The effect of the severity, duration and control of the diabetes was slight or vitiated by other factors

At present I am not entirely satisfied with the answer that arteriosclerosis is the principal cause of diabetic neuritis. There is good reason to believe that neither glycosuria nor acidosis plays a primary rôle, and in most cases none of the usual causes of neuritis can be discovered However, the extent of the degeneration seen in the nerves is by no means proportional to the degree of thickening of the walls of the nutrient arteries, and Jordan, Randall and Bloor found occasionally marked variation in the lipid content of the nerves which was unexplainable on the basis of the vascular or other known features of the diabetes. Also, if arteriosclerosis per se were the principal cause, why is this type of neuritis, with its characteristic darting pains occurring at night and relieved by exercise, not encountered more frequently in nondiabetic patients with obliterating arteriosclerosis in which the circulation is equally or more impaired?[7] An interesting cor-

[7] [illegible]

relation has been noted in the cases of neuritis, *in the clinic*, namely, that nearly always neuritis was associated with retinitis Also in the study of retinitis referred to elsewhere clear evidence of neuropathy was found in 25 per cent of cases of diabetes with hemorrhagic lesions of the retina. It existed in only 8 per cent of a control series of diabetics *without retinitis. The primary* disturbance in retinitis seems to be one of the terminal veins and possibly lesions like those observed in the retina of diabetics also occur in the veins of the nerves. The subject of diabetic neuritis demands examination of more histologic material from cases intensively studied during life before a final conclusion can be made as to its pathogenesis.

Diagnosis —The differential diagnosis of diabetic neuritis must include the ruling out of the combined sclerosis of pernicious anemia, tumor of the spinal cord and pressure on the cord from protruded intervertebral disk. In The Mayo Clinic pernicious anemia in 1937 was encountered six times among 1,184 diabetic patients and Root (April, 1933) has reported seventy-nine cases of it in the diabetic material of the Deaconess Hospital. Woltman and I from our study of three spinal cords of patients with diabetic neuritis were unable to agree with Sandmeyer and others, who stated that the degeneration of the spinal cord in diabetic neuritis is of the type seen in pernicious anemia. We found such lesions in five cases in which the two diseases, pernicious anemia and diabetes, were combined, but not in the spinal cords of patients with diabetic neuritis. The classical feature in diabetic neuritis, except for the paresthesia, is quite unlike that of the subacute combined degeneration of pernicious anemia. Ataxia is uncommon *in diabetic neuritis, and if it exists, multiple other* signs and symptoms, unusual for pernicious anemia, also will have developed.

A diabetic patient with a cord tumor, in a case described by Root (1937), seemed to have severe neuritis; however, typical

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Woltman and me or by Priestley There also was a definite correlation between [illegible] of degeneration of the nerves [illegible] c neuritis, [illegible] not [illegible] ly [illegible] n [illegible] y [illegible] of degen[illegible] occur.

Other therapeutic measures that have seemed beneficial in our experience include the administration of theobromine or its derivatives in large doses, and treatment with *sodium chloride.* We have given 10 to 15 grains (0.65 to 1 gm.) of theobromine with equal amounts of sodium bicarbonate four times a day. In some cases the oral administration of 30 gm. or more of sodium chloride, as proposed by Sandstead and Beams has provided dramatic results; in other cases this much salt has provoked such diarrhea that we could not continue using it. The procedure is still *sub judice,* and for its description the reader is referred to the article of the authors responsible for the suggestion.

Prophylaxis of diabetic neuritis demands the prescription of diets adequate in all respects and especially in the antineuritic vitamin, as well as the advice to avoid exposure to lead and other neuritis provoking substances, also moderation in the use of alcohol and tobacco. The nerves should be protected from injury. Paralysis from bed pressure may occur among patients long confined to bed, crutch paralysis must be guarded against after amputation of a leg, and all patients with diabetes should be warned against sitting with the legs crossed, to avoid injury to the peroneal nerves and consequent foot drop.

CEREBROVASCULAR ACCIDENT

The incidence of hemorrhage and thrombosis of the cerebral vessels seems to be no higher among diabetic patients than would be expected in corresponding age groups of the nondiabetic population. This is contrary to experience with arteriosclerotic gangrene and coronary occlusion. The age of diabetic individuals

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[illegible] and later by Sciclounoff and Broccard, has not been apparent [illegible] vitamin B_1 deficiency has provoked [illegible]ment, but it is not to be supposed [illegible] be similarly affected. At present information is inadequate to state how much of a rôle deficiency of vitamin B_1 may play in diabetes Sindoni demonstrated that the diets used in the clinical management of diabetes in many hospitals were on the border line of normal re[illegible] Williams and Spies to [illegible]

[illegible] associated with other diseases which are known to be due to a lack of [illegible] and (3) the realization that many diabetics subsist on diets which are low in vitamins.

suffering from apoplexy is somewhat higher and the degree of the cerebral damage resulting is less than usual. This is the conclusion of Jordan and Watters based on a study of seventy cases. At the time they made their report only thirty-one of the seventy patients were dead, and of them only six died within a short time of the accident. Of the thirty-nine patients who were living none were completely incapacitated.* I have obtained the same impression, namely, that diabetic patients tolerate cerebral hemorrhage and thrombosis unusually well. In many of our cases restoration of function has been remarkable, so much so that for many years I have found myself tempted to give a rather favorable prognosis when called to see diabetic patients because of apoplexy.

The treatment of apoplexy among diabetic patients differs from the symptomatic management usually demanded only in the necessity for continuous treatment of the diabetes. This sometimes presents difficulties, since after cerebral accidents the intensity of diabetes may be increased, necessitating larger doses of insulin, while overdosage with insulin is likely to excite more hemorrhage. Jordan and Watters have advised against lowering the blood sugar too suddenly or to too great an extent, advice which it is well to heed.

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CHAPTER XIX

COMPLICATING DISORDERS OF THE SKIN IN DIABETES

Although any of the large variety of dermatologic abnormalities may affect the skin of patients with diabetes, the incidence of association with diabetes of most of them does not seem to indicate any unusual predisposition on the part of diabetic patients. The disorders selected for consideration, either because of possible etiologic relationship or because they are encountered more frequently among diabetic patients than among others, include hirsutism, rubeosis, xanthosis, xanthomatosis, necrobiosis, pruritus, trichophytosis and pyogenic infections. Abnormalities attributable to injections of insulin, such as insulin atrophy and insulin allergy, have been described in Chapter VI.

HIRSUTISM

Hirsutism is found in patients who exhibit the pituitary and adrenocortical syndromes, described in Chapter XVI. The "diabetes of bearded women" of Achard and Thiers possibly can be explained on the basis of excess or abnormality of adrenal cortical hormone The fine, downy, lanugo hair, particularly of the back, frequently encountered in neglected cases of juvenile diabetes, is almost always a sign of malnutrition and disappears after nutrition is improved The epithelial layer of the skin of such patients often is thin and unusually translucent.

RUBEOSIS

The term "rubeosis" was applied by von Noorden to a peculiar rosy coloration of the skin of the face, which often is seen in the presence of neglected diabetes among the young. The hands and feet may be affected, but the forehead and cheeks are the usual sites The eyebrows may be stunted, sparse or absent. Diminished tone with consequent lengthening and broadening of capillaries has been described for the capillaries of the nail fold of the fingers of younger persons with diabetes, and it is suspected that

similar capillaries in the skin affected with rubeosis, combined with an abnormal transparency of the epidermis account for the color. Under treatment the tone of the capillaries increases and the coloration of the skin disappears (von Noorden and Isaac). Association of rubeosis with the xanthosis, to be described later, imparts the "peaches and cream" complexion which so frequently is seen in the presence of neglected diabetes among young persons, and sometimes is mistaken for a bloom of health.

XANTHOSIS

Von Noorden likewise was first to call attention to a yellowish dermal discoloration of the skin frequent in diabetes (von Noorden and Isaac). He thought that it was a manifestation of diabetes and therefore called it diabetic xanthosis However, Salomon, in 1919, recognized the dependence of the pigmentation on the intake of pigmented foods, such as vegetables, fruits, butter and eggs, and that the condition in diabetic patients was not dissimilar to the pseudo-icterus which Moro in 1908 had described as developing in nondiabetic children when carrots were added to their diets Furthermore, Salomon demonstrated that the pigments, found by van den Bergh and Snapper in the blood of diabetic patients with yellow skin and spectroscopically identified by them as plant pigment, also could be found in the skin of nondiabetics, both with and without accompanying discoloration of the skin. He applied the term "xanthemia" to the circulation of pigments in the blood and the term "xanthosis" to their deposition in the skin, and recognized that xanthemia could occur in the absence of apparent xanthosis but that xanthosis always is accompanied by xanthemia.[1]

The yellow pigmentation of the skin known as xanthosis, or

[1] Bibliographic references and excellent reviews on the subject of xanthemia and xanthosis are to be found in papers by van den Bergh and Muller (1920), Palmer (1920), Greene and Blackford (1926), Stoner (1928) and Stannus (1929), all of them cited by Boeck and Yater

The terms "carotenemia" (carotinosis) of Hess and Myers (1919) and "carotenosis" (carotinosis) of Moro (1908) and Miura (1917) are unsatisfactory. Although the chief yellow lipochrome present in the blood serum has been iden- [illegible]

pigments.

carotenosis, is most marked in the palms, soles and nasolabial folds, whereas, in contrast to jaundice, the sclerotics usually remain clear. The differential diagnosis of xanthosis and jaundice depends on the history and other findings, a knowledge of the patient's diet, the concentration of bilirubin in the serum, the icterus index and the lipochrome index (Boeck and Yater). When with yellow pigmentation of the skin a low value for the serum bilirubin and a high icterus index are present, the condition must be xanthosis; if the value for the serum bilirubin is high and the lipochrome index is low, the abnormal coloration is due to jaundice, whereas if both the concentration of serum bilirubin and the lipochrome index are elevated, xanthosis and jaundice are associated.

Boeck and Yater in The Mayo Clinic found the xanthophyll pigments of the blood serum increased (xanthemia) in eighty-six (86 per cent) of 100 consecutive hospital patients with diabetes. In nine of them xanthosis was apparent, being correlated roughly with the degree of associated xanthemia. Xanthosis never was seen without xanthemia. The presence, in the diet, of foods containing pigments is the factor of primary importance in the production of these conditions, but other factors also must be involved since many patients on diets rich in fruits, vegetables, eggs and butter fail even to show evidence of xanthemia. It is probable that individual variation occurs in the ability of persons to oxidize and excrete these pigments.

The nine patients with xanthosis in the series of cases of diabetes studied by Boeck and Yater, represented for the most part patients who had severe diabetes, but the evidence obtained then or subsequently does not warrant the conclusion that the presence of xanthosis affects unfavorably the course of diabetes,[2] nor

[2] Heymann, however, after determining the content of carotene in the blood serum at intervals after the administration of carotene in oil to ten diabetic and twelve nondiabetic children, concluded that carotene metabolism is interfered with in diabetes, and Stueck, Flaum and Ralli have come to the same conclusion. They explained that the difficulty is due to failure of the liver to convert carotene to vitamin A, but offered what seemed to me insufficient evidence to establish such a conclusion. Later Brazer and Curtis compared biophotometric studies on a series of twenty juvenile diabetic patients with studies on twenty interns and hospital staff members, and noted a definite reduction in the readings of the diabetics. Xanthemia was present in all of them. They further found that feeding 60,000 units of carotene daily for seven days to seven of the diabetics, although it increased the blood carotene levels, did not cause improvement in their biophotometer readings, while giving 60 000 units of vitamin A, as halibut oil, for seven days, caused

has there been any clear correlation between the presence or degree of xanthemia and the lipoid content of the blood except in cases of acidosis with marked lipemia.

That xanthemia and xanthosis, in patients with diabetes, are not strictly related to diabetic abnormalities of metabolism was shown by Boeck and Yater, who found xanthemia in all of twenty-two patients with renal disease, in thirteen of nineteen patients with hepatic disease, and in sixteen of twenty-three other hospital patients selected at random. As was stated, xanthosis was present in nine of the 100 patients with diabetes. It was also found in two of the patients with renal disease and in one of the other nondiabetic patients.

The presence of xanthosis, although it does not affect the course of diabetes or the health of patients, is sometimes of sufficient intensity to cause embarrassment. The treatment of the condition depends on restricting the intake of pigmented fruits and vegetables. It rarely is necessary to limit the intake of eggs and butter. These restrictions necessitate provision of vitamins in the form of concentrates—brewers' yeast, thiamin chloride, a vitamin A concentrate—and separate administration of calcium and iron.

XANTHOMATOSIS

It is somewhat questionable to my mind whether there is justification for distinguishing a diabetic type of xanthoma. This lesion, as seen in cases of diabetes, is a symptom of hyperlipoidemia and, in addition to occurring with diabetic hyperlipoidemia, is encountered with hyperlipoidemia in biliary cirrhosis and in cases of so-called essential hyperlipoidemia. It is a tuberous xanthoma predominantly situated on extensor surfaces, as distinguished from the disseminate variety usually found on flexural surfaces,[*] a yellow or salmon-colored, shotty nodule, from one to

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a return of the readings to near normal After the dose of vitamin was discontinued rapid regression occurred The findings substantiated the previous conclusions of others that diabetics are less able than normal persons to convert carotene to vitamin A

[*] For excellent discussions of this subject the reader is referred to articles by Montgomery, Thannhauser and Magendantz, and Montgomery and Osterberg. Less common than the tuberous form of xanthomatosis is the so-called disseminate form This is characterized by multiple fine papular lesions of the skin which predominate on flexural surfaces, but also, in contrast to xanthoma tuberosum involve mucous membranes and at times bone, with encroachment on the pituitary body and the brain (Hand-Schüller-Christian syndrome). In contrast to the tuberous

several millimeters in diameter, which on microscopic examination is found to consist mainly of large cells filled with lipoids, so-called foam cells. The cutaneous lesions of tuberous xanthomatosis are symmetrically distributed, but have a predilection for the hands, feet, knees and elbows. Frequently they also are found at the sites of scars. The face and neck usually are spared, although there is reason to believe that the histologically similar, but much more common, lesion of the eyelid, known as xanthelasma, is a closely related abnormality.

The degree of lipoidemia associated with these lesions of the skin is represented by values for cholesterol, phospholipoid and fatty acid in the blood which are from two to five times the upper limits of normal values In all such cases the xanthomas can be made to disappear if the hyperlipoidemia can be controlled

The ability of the intestine to excrete cholesterol varies with the species and also with individuals within the human species. Herbivorous animals, while capable of absorbing cholesterol, are at a handicap, compared to carnivora, in ridding themselves of any excess of it. This explains the ease with which hypercholesteremia with consequent atheromatosis is obtained by feeding animal fats to rabbits The sterols of plants are not absorbed and in essential hyperlipoidemia of man, to which affliction relatively few individuals of the human species are susceptible, irrespective of the presence or absence of diabetes, control of the hyperlipoidemia, and of the xanthomatosis which may accompany it, can usually be obtained by making the diet free from animal fats. Hyperlipoidemia in man is not always accompanied by cutaneous xanthomatosis. Notable examples with extremely high values for blood lipoids and no cutaneous lesions have come to our attention Thus, factors other than hyperlipoidemia, possibly local in the skin, such as injury (scars) or dehydration by diabetic acidosis, may play a part in creating the xanthomas.

In all of this the only way in which diabetic xanthomatosis seems to differ from xanthoma tuberosum with hyperlipoidemia,

form the disseminate form of xanthoma is not associated with abnormal values for blood fats and the cutaneous lesions are not influenced by dietary procedures On the other hand, the histologic appearances of the tuberous and disseminate forms of xanthoma are indistinguishable, and chemical analysis of lesions of both types by Montgomery and Osterberg revealed "definite proportionate increase in cholesterol content, reaching as high as 64 per cent of the total lipoids and dropping to 18 per cent only in one old fibrous nodule which histologically revealed very few foam cells"

but without diabetes, is in the greater rapidity with which the lesions sometimes develop and under treatment disappear. Cutaneous xanthomatosis probably is no more common among diabetic than among nondiabetic patients. It was recorded in only eleven of Joslin's many diabetic patients, and I think this number would about represent the frequency of the condition in our experience. Only five instances of xanthoma diabeticorum were found by von Noorden in his enormous number of cases of diabetes (von Noorden and Isaac), and Major noted only eighty genuine cases in the literature.

In diabetic xanthomatosis the diabetes usually is severe, with recurring episodes of acidosis; in my experience it always has been associated with hyperlipoidemia. In Joslin's cases in which values for plasma cholesterol were obtained the values were grossly abnormal in all but one case, varying from 0.344 to 1.600 gm. per 100 c.c. Treatment with insulin in cases in which the hyperlipoidemia depends on uncontrolled diabetes and acidosis may effect involution and disappearance of the xanthomas in a few weeks. The patient, however, should be watched for recurrence and should be given a diet low in animal fat (see p. 120). The low fat diet is recommended less because of any harm from recurrence of the lesions of the skin than because of the frequency with which severe grades of atherosclerosis have been encountered in other forms of severe hyperlipoidemia.

NECROBIOSIS LIPOIDICA DIABETICORUM

A cutaneous lesion which promises to appear among diabetic patients more frequently than xanthoma is *necrobiosis lipoidica* diabeticorum. This condition develops predominantly in cases of diabetes. It was first described in 1929 by Oppenheim and received this name in 1932 from Urbach. My associates, Hildebrand, Montgomery and Rynearson studied eight cases; the first seven were seen in a period of two and a half years, among approximately 3000 diabetic patients. A complete bibliography of the subject is given in their paper.

The lesions of necrobiosis lipoidica diabeticorum traverse several phases. Initially, a reddish papule appears, 1 to 3 mm. in diameter. This very slowly increases in size, becoming violaceous and later is transformed into a raised, firm, yellowish or apple-jelly

colored plaque with a waxy surface several millimeters or 1 or 2 cm. in diameter. The plaque softens in the center and may ulcerate. It ultimately gives way to a flattened atrophic lesion several centimeters in diameter, surrounded by a red or violaceous region of infiltration. Such lesions are single or multiple and are seen in various stages of development. The common sites are on the legs below the knees, although cases have been reported in which they have been situated on the arms, hands, trunk and face. New lesions appear, grow very slowly and ultimately seem to reach a quiescent stage; they do not progress indefinitely but do not heal, despite rigid diabetic control. They differ from xanthomas in this respect, and also by the fact that they are not associated with any gross elevation of values for the lipoids of the blood. They can be clearly distinguished from tuberculosis and other cutaneous abnormalities by histologic examination. The lesion of diabetic necrobiosis is one of the corium, with swelling of collagen fibers and proliferation of the cells of the blood vessels. Lipoid deposits are seen, but these are mostly extracellular and fail to show double refraction. They stain reddish brown with sudan III. Foam cells and giant cells are absent. The dermatologists who have described the condition have assumed for the most part that the primary lesion was in the vessels of the corium, but in the cases coming to our attention all palpable peripheral vessels have been patent and the arterioles and vessels of the fundus of the eye appeared normal.

Diabetic necrobiosis is much more common among women than among men The ratio in about eighty-seven cases heretofore reported has been about 4:1 The commonest age at which the skin lesions first appeared seems to lie between ten and forty years Trauma may play a part. In at least one of our cases and in many reported cases the first lesion was thought to have appeared at the site of a previous scratch or bruise, and in two of our cases a lesion in the papular stage progressed rapidly to the stage of ulceration following trauma.

No effective treatment has been found for necrobiosis lipoidica diabeticorum, but good control of the associated diabetes is important as is evidenced by the fact that the diabetes in many cases has been poorly controlled throughout its course.

PRURITUS

The pruritus of the external female genitalia has been considered in Chapter XIII. It is a frequent complaint of women with uncontrolled diabetes, and represents a serious complication. Otherwise pruritus in cases of diabetes is today uncommon. Localized itching, similar to the pudendal pruritus of the female, and like it dependent usually on local trichophytosis, is sometimes seen in men and causes balanitis and phimosis. Pruritus from a similar cause sometimes involves the scrotum and anus. Control of glycosuria and cleanliness in almost all cases are all the treatment necessary Exposure to roentgen rays is to be avoided.

General pruritus is very rarely encountered other than in cases of uncontrolled severe diabetes and dehydration. It may, however, be the first symptom of diabetes to attract attention. If it persists when the diabetes is under control, as it very rarely does among older patients, it may represent a symptom of arteriosclerosis. In such cases the use of insulin may aggravate the itching and make it desirable to depend only on the diet. Sodium or acetyl salicylate administered orally often is beneficial. This treatment was recommended by von Noorden, who also made use of a salve containing 5 per cent of calcium chloride. He warned repeatedly against attempts at treatment with roentgen rays (von Noorden and Isaac).

INFECTION

"Athlete's foot."—The importance of guarding against fungus infection of the feet is emphasized in Chapter XXII. The peculiar susceptibility of diabetic patients was pointed out by Greenwood. A safe treatment is to soak the feet for thirty minutes, twice daily, in a freshly made 1:8000 solution of potassium permanganate

Pyogenic infections of the skin.—Diabetic patients are more susceptible than others to infections and must be cautioned to keep the skin and clothing clean. Dirty collar bands and the use of dirty towels and dirty razors are the more common causes of furunculosis. At Dr. William J. Mayo's suggestion, we long have advised our diabetic patients to shave themselves and when the hair is cut to instruct the barber to omit the customary shaving of the neck.

The application of strong antiseptics to the skin should be avoided. Tincture of iodine, solution of bichloride of mercury, carbolic acid and medicated salves are considered especially dangerous. Localized infections such as furuncles are treated best by immobilizing the part and applying large, wet compresses saturated with equal parts of 50 per cent grain alcohol and saturated solution of boric acid (see Chapter XII).

DUPUYTREN'S CONTRACTURE

Contraction of the palmar fascia, encountered usually only among older persons, seems to occur more frequently than usual among patients with diabetes. Only two instances of this condition had been recorded on the diagnostic sheets of the 1184 diabetic patients seen in the clinic in 1937, but the incidence of the abnormality is much higher than this I am sure. It causes little inconvenience and in most cases escapes formal recording. Teschemacher observed it in thirty-three of 1900 cases of diabetes Its cause is uncertain, but if it represents an inflammatory reaction of the palmar fascia, as is supposed, it apparently is the only type of fibrositic or rheumatic affection which occurs with unusual frequency with diabetes. Treatment is surgical, as described by Kanavel and his associates.

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CHAPTER XX

COMPLICATING DISORDERS OF THE DIGESTIVE ORGANS IN DIABETES

TEETH AND TONSILS

There is ground for strong suspicion that focal infection in teeth and tonsils plays an important part in the cause and course of diabetes. Proof for this admittedly is lacking, but we may rightly suppose that the pancreas, like other organs, suffers injury, either by metastatic infection or from toxic substances released from chronic abscesses wherever they may be. This perhaps never precipitates diabetes mellitus in persons not predisposed genetically to insular failure, but it may well do so when the stage previously has been set by heredity. Once diabetes has developed, in any individual, or from whatever cause, its progression and intensity are well known to be increased by sepsis. Therefore with diabetic patients the teeth and tonsils, which more frequently than other sites are likely to harbor infection, ought to be given suitable attention, and the same advice applies to the blood relatives of diabetic patients, as a part of the effort to prevent the development of diabetes.

In the pre-insulin era caries and pyorrhea were notorious offenders in diabetes, and today they usually are encountered when the management of diabetes is poor. The lowered resistance of the teeth under such conditions is easily explained by malnutrition, dehydration and acidosis. When insulin is used and the diet is nutritionally adequate, we frequently have found that diabetic children have sounder teeth than their nondiabetic brothers and sisters whose diets received less attention. Marble made a similar comment and cited the observation of Boyd and Drain that dental caries of diabetic children was arrested when adequate provision was made for controlling the diabetes. It is not surprising. Nutritionists have long demonstrated the importance of the diet in the development and resistance of the teeth of animals. It merely adds further emphasis to the importance of including

liberal allowances of vitamins, calcium and all other nutritional factors in the diets planned for human beings.

Oral hygiene also must be emphasized, especially the regular brushing of teeth and massaging of the gums. It is astonishing how many people, clean otherwise, are shameless about dirty mouths Likewise, regular visits to a dentist must be demanded, at least twice each year, for attention to accumulations of tartar, to which diabetes predisposes and for early filling of cavities

When teeth die their removal should be recommended, with replacement by bridges which will not injure the living teeth that serve as abutments. If periapical regions of resorbed bone are detected, extraction is imperative, but as in all operations, precaution must be taken before and after operation to avoid acidosis. If this is done, the risk is negligible. We never have had a death from extraction of teeth, in all the years since insulin became available.

Tonsillectomy is advised if the patient gives a history of frequent sore throat or, in the absence of such a history, when the tonsils are grossly abnormal, with deep crypts from which pus can be expressed. This operation also can be done with minimal risk provided, as always, precautions are observed to avoid acidosis and also if the patient is confined to the hospital until the throat is well on the way to complete healing. In 153 cases of diabetes in which tonsillectomy has been performed in recent years three deaths occurred. In two cases, however, the deaths were due to other associated diseases. The third patient left the hospital the day after operation and took no care of himself; subsequently an overwhelming infection developed.

THE ESOPHAGUS

Simple diffuse ulceration of the esophagus is seen not infrequently at necropsy; in all probability postmortem digestion is responsible. It rarely, if ever, is encountered in life without some accompanying evident provocative disease. Such a lesion discovered on esophagoscopic examination of a diabetic patient, who complained of esophageal symptoms, was described by Vinson and me. It consisted of extensive annular ulceration with little, if any, reduction of the lumen of the esophagus. The lesion was covered with necrotic membrane and bled easily The

patient had had severe and badly neglected diabetes for five years, but no other disease. Repeated serologic tests for syphilis gave negative results. Local treatment with silver nitrate relieved the symptoms, but did not effect a cure of the lesion. At necropsy, two years later, no evidence of syphilis could be found and the esophagus still showed thickening and numerous regions of superficial ulceration. A similar ulcerative lesion was found by Dr Vinson in another of our diabetic patients, but in this case, with local treatment and diabetic control healing was obtained. The patient had complained of hoarseness for seven months Diabetes, potentially mild but uncontrolled, probably had been present for three years. A serologic test for syphilis gave negative results.

THE STOMACH AND DUODENUM

Peptic ulcer was diagnosed in sixty-one (2.3 per cent) of the 2,584 separate cases of diabetes seen in a three-year period (1935 to 1937 inclusive) and carcinoma of the stomach was recognized in an additional twenty-three (0 9 per cent). That this incidence of ulcer represents any unusual predilection in diabetes for gastric or duodenal ulcer appears unlikely. The incidence actually seems to be much lower than that among the nondiabetic population, because among all patients who were examined at The Mayo Clinic in 1937 the incidence of duodenal ulcer was 3 5 per cent. In former years peptic ulcer was even less common in diabetes than now In Joslin's first 2,700 diabetic patients—seen before 1922—also in Falta's experience, not a single case of ulcer was encountered. The explanation may lie in the frequency of anacidity in uncontrolled diabetes Marble, adding the data of several investigators, found that 32 8 per cent of 399 diabetic patients examined had complete anacidity. Eusterman and Balfour found the incidence of anacidity in general to be from 10 to 15 per cent of all persons examined

If the base of a chronic penetrating ulcer becomes adherent to the pancreas, it may provoke an inflammatory pancreatitis and severely aggravate an existing diabetes Although I cannot recover the record, I distinctly remember a case in which a middle-aged diabetic patient periodically had episodes of severe epigastric pain. This extended to the back A penetrating duodenal ulcer was clearly revealed by roentgenologic examination. The patient

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THE COLON AND RECTUM

The diseases of the intestine encountered among diabetic patients are not unusual in frequency of occurrence or in character. The peculiar diagnostic problem presented by appendicitis has been referred to in Chapter XII. I am impressed, however, by what seems to be an increasing incidence of carcinoma of the colon and rectum. In the 2,584 cases of diabetes observed in the period 1935 to 1937 inclusive, were twenty-one instances of carcinoma of the large intestine and twenty-one instances of carcinoma of the rectum In approximately an equal number of cases of diabetes encountered from 1924 to 1928 inclusive, carcinoma of these organs occurred with only about a third this frequency. Age of the patients may account for the increased incidence; the average age at admission of all diabetic patients in the more recent period was greater by 5.6 years. The figures for all carcinomas seen in the two series of cases indicate that between the periods mentioned the general incidence of malignancy rose from 4.8 to 7.8 per cent. With very few exceptions the growths were carcinomatous. The most common sites of the 202 carcinomas observed in the more recent period were as follows: the stomach in twenty-three, colon in twenty-one, pancreas in thirteen, and rectum in twenty-one cases. The exceptionally high incidence of carcinoma of the pancreas is noteworthy.

A disturbing feature of carcinoma of the colon and rectum is that operation for these lesions among diabetic patients has been attended by a mortality almost three times as great as that encountered among patients who were not diabetic. This, I think, is

incidence of 1.3 per cent of cases of carcinoma of the pancreas among 52,509 deaths from cancer among policyholders of the Metropolitan Life Insurance Company. Possibly some relationship exists between the relatively high incidence of carcinoma and the greater frequency of fibrosis in the diabetic pancreas The fibrosis, as Warren has suggested, presents a rather striking analogy to the process of cirrhosis of the liver, which not infrequently leads to primary malignancy of the liver.

Syphilis.—Syphilis of the pancreas was not once encountered in the 484 diabetic necropsies reported by Warren, nor in the 201 postmortem examinations of diabetic patients made at The Mayo Clinic. Citations of reports of both interstitial and gummatous pancreatitis have been given by Falta and by Warren.

Instances of recovery from syphilitic diabetes have been reported by Umber, and Paullin and Bowcock. Von Noorden and Isaac, in about 100 cases of diabetes in which antisyphilitic measures were employed, could recall only three in which "perhaps" something more was effected than the dietetic treatment which the patients were receiving could accomplish. The presence of positive serologic reactions in cases of diabetes has been *extremely unusual in our experience (an incidence of less than* 1 per cent), and I can recall very few cases in which the patient has manifested any of the common sequelae of syphilis such as tabes dorsalis or paresis

Calcification and cysts —Three instances of pancreatic lithiasis were mentioned by Warren and three instances appeared in the report of fifty-eight diabetic necropsies which I reviewed. J G Mayo found twenty-five proved cases of pancreatic lithiasis in the records of The Mayo Clinic. Diabetes was frequently associated with lithiasis in these cases The condition had been diagnosed during life in only a few No treatment is available for stones in the ducts or calcification of the substance of the pancreas. Some cysts of the pancreas attain enormous size and compress the pancreatic tissue enough to provoke insular insufficiency in persons with otherwise normal insular reserves In such cases the diabetes sometimes can be cured by operative attention.

Diarrhea.—Chronic diarrhea, in cases of diabetes, may depend on any of the ordinary causes of diarrhea In the past much of it resulted from the bulkiness of diets and the popularity of bran

creatitis precede the onset of the diabetes. Other lesions of the pancreas in cases of diabetes include carcinoma, syphilis, calculi and cysts, all rare with the exception of the first.

Carcinoma.—Carcinoma in the diabetic population seems to be on the increase, with carcinoma of the pancreas assuming a position almost as important as carcinoma of the stomach. At The Mayo Clinic pancreatic carcinoma was found in six of 139 cases of diabetes which came to necropsy between October 1, 1925, and December 31, 1936 inclusive, whereas in fifty-eight necropsies in

TABLE 8

CHANGES FOUND IN THE ISLANDS OF LANGERHANS AT NECROPSY IN CASES OF DIABETES AND IN CASES IN WHICH DIABETES WAS NOT PRESENT

Authors	Cases	Fibrosis.	Hyaline degeneration
	Cases of diabetes		
Cecil	90	49	27
Gibb and Logan	142	79	30
Herxheimer	97	13	38
Warren	484	129	200
Dry and Tessmer	201	98	73
Total	1014	368	368
Per cent of total	.	36	36
	Cases in which diabetes was not present		
Warren	200	15	4
Dry and Tessmer	50	4	1
Total	250	19	5
Per cent of total		7 5	2

the preceding six years only one carcinoma of the pancreas was found. Also, as was stated before, thirteen carcinomas of the pancreas were diagnosed clinically in the three-year period, 1935, 1936 and 1937, representing nearly 7 per cent of all cases of diabetes with carcinoma.[1] At the George F. Baker Clinic the figures given by Marble for carcinoma of the pancreas represented 13 cent of all cases of carcinoma. This he contrasted to the

[1] Cases of carcinoma of the pancreas represented only 1 7 per cent of all cases of carcinoma encountered in The Mayo Clinic in the year 1937.

every two to three hours day and night, the stools being light brown, soft to liquid, frothy, fatty and uncommonly offensive Treatment was begun with the preparation of pancreatic juice. Within twenty-four hours the number of stools had been reduced to four a day and in a few days they were quite normal. It was later found that normal intestinal function could be maintained only by the continued administration of a minimal amount of the dried juice.

THE LIVER AND GALLBLADDER

In view of the important part played by the liver in carbohydrate metabolism, it is surprising that so little clinical evidence of hepatic disease is encountered in most cases of diabetes mellitus. Cirrhosis is very uncommon. Evidence of it or of hepatitis was encountered at The Mayo Clinic in only seventeen (0 7 per cent) of our 2,584 separate cases of diabetes in the years 1935, 1936 and 1937, and when hepatic disease was found it seemed rarely to be related to the diabetes or to affect it seriously.[3] I have not met with catarrhal icterus, although Falta cited Dibold as observing it in eleven of 224 cases of diabetes in which the patients were males but not in 200 cases in which the patients were females. Falta had seen it not infrequently among both sexes.

Hepatomegaly.—In untreated or poorly controlled diabetes, particularly of children, enlargement and tenderness of the liver from infiltration with fat often has been encountered at the clinic. Possibly, as Warren has suggested, there also may be an increase in the intercellular water of the liver in such cases, and the tenderness in part may be caused by stretching of the capsule. In them, however, there seldom is impairment of any measurable function of the liver; furthermore, the disturbance soon is corrected when satisfactory diabetic control has been obtained. Large fatty livers develop with regularity in depancreatized dogs, unless the animals are given raw pancreas with their food (Allan) or lecithin (Hershey), choline or betaine (Best) or lipocaic (Dragstedt). The analogy naturally has led to the suggestion that the overlarge liver found in cases of uncontrolled diabetes may be attributed to the

[3] I have referred elsewhere to the cases of Lande and Pollock in which correlation was observed between the degree of glycosuria and that of impairment of hepatic function Six somewhat similar cases were later reported by Conn, Newburgh, Johnston and Sheldon The disturbance of carbohydrate metabolism was characterized by low values for blood sugar during fasting—often extremely low—but by hyperglycemia and glycosuria after ingestion of carbohydrate. Studies of the respiratory quotient provided no reason to believe that combustion of sugar was disturbed. Such cases in their opinion have been wrongly interpreted as examples of diabetes mellitus, hyperinsulinism and dysinsulinism.

as a substitute for food. Those days fortunately are behind us; nevertheless, occasionally an intractable diarrhea is encountered for which no satisfactory cause can be ascertained. Bargen, Bollman and Kepler have ventured to call this the "diarrhea of diabetes." It may have no relation to diabetes, as they admitted, but it is unusual and resistant to treatment. In searching for a cause the pancreas naturally has been under suspicion, even though *evidence suggestive of failure of its external secretion* could not be obtained. Administration of pancreatic preparations or even of a very active pancreatic juice, however, has not been of any benefit. It is a serious complication, not only because of the malnutrition it produces, but also because irregular absorption of food adds greatly to the difficulty of estimating the necessary doses of insulin.

Steatorrhea, as evidence of failure of external pancreatic function, is not as common in cases of diabetes as might be supposed. Indeed it occurs infrequently. When it is encountered its treatment is difficult. Commercial preparations of pancreas for the most part have been ineffective [2] The following typical example of pancreatic failure in which treatment with a desiccated preparation of pancreatic juice obtained from dogs with pancreatic fistula proved beneficial was cited in a report from the clinic by Bargen and his associates:

The patient, an unmarried man thirty-six years old, had had upper abdominal pain for eight years This came in attacks which lasted four or five days, and left interval soreness It extended to the back, was associated with distention of the abdomen, chills and fever, and sometimes with vomiting Morphine was required to relieve it. The feces for a long time had been green and foamy and floated on water They were numerous and bulky. Diabetes had been discovered six weeks before the patient came for consultation to The Mayo Clinic and insulin in a daily dosage of 40 units was used.

On examination at the clinic the urine contained sugar, the concentration of blood sugar was elevated and roentgenograms revealed extensive pancreatic lithiasis. Results of tests of liver function and filling of the gallbladder were negative, as also were those of the serologic tests for syphilis At operation a large indurated pancreas with calcification was found Four months later the patient had much less pain but continued to have bowel movements

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of liver function. These conditions were not improved by better control of the diabetes, but did respond to treatment with lipocaic. Specimens of the liver secured at operations before and after treatment with lipocaic also revealed disappearance of fat.[4]

Gallstones—Cholecystitis, with or without, but mostly with, gallstones, was diagnosed in 139 (5.4 per cent) of the 2,584 separate diabetic patients observed in the clinic in the years 1935, 1936, and 1937. This figure, with rare exceptions, represents only cases in which the disturbance had given rise to symptoms, because in sixty-six (33.5 per cent) of 197 cases of diabetes in which necropsy was performed at the clinic from October 1, 1919 to December 31, 1936 inclusive (139 reported by Dry and Tessmer and fifty-eight previously by me), gallstones either were present or had been removed by an operation. The figures reveal that a great many gallstones are carried inconspicuously to the grave Comparative statistics for necropsies on nondiabetic patients vary widely At one extreme is a report by White (White, Robson and collaborators) that gallstones were found in only 3 per cent of 11,031 necropsies at Guy's Hospital and at the other is Mentzer's report that gallstones occurred in 21 per cent of 600 necropsies at The Mayo Clinic. Warren's figure for the incidence of gallstones in 453 cases of diabetes in which necropsy was performed on patients who were more than thirty years of age was 31 per cent, and that for 500 consecutive necropsies on nondiabetic patients in the same age group was 21 per cent. Thus cholecystic disease, or at

[4] In this connection certain recent observations bearing on the rôle of the alpha cell of the islands of Langerhans are of great interest. They were made by disciples of that grand old student of the pancreas, who for forty years has headed the department of anatomy at the University of Chicago, Robert Bensley Woerner, in the last of a [illegible]

[illegible]

central vein

In previous studies by Bensley and Woerner, the suggestion was made that the alpha cells [illegible]

[illegible]

Dragstedt and his co-workers

absence of something other than insulin, which normally is supplied by the pancreas. However, that this is not true in most cases was shown by White, Marble, Bogan and Smith, who gave raw pancreas to two diabetic children and betaine to twelve children who had hepatomegaly. No significant change in the size of the liver was observed with feeding of raw pancreas, and more or less diminution occurred in only six (50 per cent) of the patients receiving betaine. On the other hand hepatomegaly was corrected in fifteen (nearly 80 per cent) of nineteen children who received nothing except protamine insulin, which controlled their diabetes. In our own experience I cannot recall a single case of hepatomegaly of the type described in which the patient failed to respond to satisfactory control of the diabetes with diminution of the size of the liver.

This clinical experience provides little reason to believe that deficiency of lipocaic or other secretion of the pancreas involved in fat metabolism is a practical problem in diabetes, except perhaps in those rare cases of diabetes in which the pancreas as a whole is destroyed by gross disease. However, Dragstedt and his associates recently emphasized that two types of fatty infiltration are encountered in experimental pancreatic diabetes, and possibly also in clinical diabetes. One type is due to poor control of the diabetes because of inadequate administration of insulin. This is characterized by a normal or high concentration of the lipoids of the blood and by acidosis. The second type is due to lipocaic insufficiency. It is accompanied by a low concentration of the blood lipoids, impaired hepatic function, increased sensitivity to insulin and decreasing requirements for insulin. The first type s relieved by insulin, but not the second. That fatty infiltration nd enlargement of the liver of the second type also occurs in uman diabetes, is suggested by three cases reported by Grayzel nd Radwin, and one reported by Rosenberg. The patients of Grayzel and Radwin were young diabetics with hepatomegaly. Their diabetes was well controlled with diet and insulin. The arge livers diminished in size when lipocaic was administered, ncreased in size when lipocaic was withheld, and again diminshed in size when treatment with lipocaic was resumed. The atient in Rosenberg's case was an adult with mild diabetes. Hepatomegaly was marked and was associated with impairment

also because of the danger of the development of diabetes. To diabetic patients our advice is to have the gallstones removed when the conditions of time, place, surgeon and physician are propitious."*

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CHAPTER XXI

HEMOCHROMATOSIS

In hemochromatosis we have to deal not with a complication of diabetes mellitus, but with a cause of it. Hemochromatosis is a disorder of pigment metabolism, probably inborn. It is characterized by large accumulations of the ferrous compound, hemosiderin, and the nonferrous compound, hemofuchsin, in the liver, pancreas, spleen and other organs and tissues, by bronzing of the skin, cirrhosis of the liver and pancreas, and frequently, but not always, by diabetes mellitus The relationship of the diabetes is clearly dependent on the degree of affection of the pancreas. In cases with little or no cirrhosis of the pancreas, diabetes is not encountered, whereas with severe pancreatic involvement it invariably appears [1]

INCIDENCE

Sheldon's excellent monograph, published in 1935, is based on an intensive search of the literature. References, many of them to provincial journals of various countries, provided information relative to a total of 345 ostensible cases. Of them 311 were accepted as genuine. The disease, therefore, is rare, although not so rare as formerly was assumed. Butt and I reported

[1] "The first undoubted case [of hemochromatosis] in the literature appears to be that described by Trousseau in 1865 in the course of a clinical lecture on glycosuria, but no special name was then attached to the syndrome The next case was described by Troisier in 1871 under the title of 'La Cirrhose pigmentaire dans le diabète [illegible]
gested. [illegible]
sucré' [illegible]
1886); [illegible]
le diat [illegible]
pigmer [illegible]
Tolot, [illegible]
and Sc [illegible]

"Of the three chief synonyms, two derive from France (bronze diabetes and pigment cirrhosis) and one from Germany (hæmochromatosis) . . .

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INCIDENCE

Sheldon's excellent monograph, published in 1935, is based on an intensive search of the literature. References, many of them to provincial journals of various countries, provided information relative to a total of 345 ostensible cases. Of them 311 were accepted as genuine The disease, therefore, is rare, although not so rare as formerly was assumed. Butt and I reported

[1] "The first undoubted case [of hemochromatosis] in the literature appears to be that described by Trousseau in 1865 in the course of a clinical lecture on glycosuria, but no special name was then attached to the syndrome. The next case was described by Troisier in 1871 under the title of 'La Cirrhose pigmentaire dans le diabète [illegible]
gested, [illegible]
sucré' [illegible]
1886), [illegible]
le diat [illegible]
pigmer [illegible]
Tolot, [illegible]
and So [illegible]
"C [illegible]
pigment cirrhosis) and one from Germany (hæmochromatosis) .

"The discussion on the exact relations of the conditions described by these terms has been mainly conducted in France and Germany A comparison of the titles of papers with their subject-matter leaves no doubt that for many years most authors in England and America have regarded the terms as synonymous" (Sheldon).

on thirty cases observed at The Mayo Clinic in fifteen years. In these the diagnosis, supported in each instance by microchemical demonstration of iron in sections of skin removed for biopsy, had been made clinically. In the same period of fifteen years, the diagnosis had been made in two cases at necropsy.[2] Althausen and Kerr (1927) found three cases of hemochromatosis in 60,000 admissions to the University of California Hospital, and three among 106,000 admissions to the Johns Hopkins Hospital. In the reports on the subject by pathologists, a higher incidence than this frequently is suggested, but the question arises whether pathologists, in cases of cirrhosis of the liver of more common types, always have distinguished between hemochromatosis and hemosiderosis.

Striking features in hemochromatosis are the incidence as to sex and age. The patients in only thirteen of the 311 cases collected by Sheldon were women, and in the thirty cases (the number at the present writing is thirty-four) observed in The Mayo Clinic only one of the patients was a woman. The distribution by age is equally singular. The patients in 77 per cent of Sheldon's 311 cases were more than thirty-five years of age; only ten were younger than thirty years and none were younger than twenty years. In the cases reported by Butt and me the youngest patient was aged twenty-seven at the time of diagnosis and thirty-one at death; all of the others in our series were aged thirty-seven years or more at the time of diagnosis.

ETIOLOGY AND PATHOGENESIS

The existence of a familial or hereditary character in hemochromatosis is supported by several instances of occurrence of the disease among brothers (Sheldon). In a family described by Lawrence (1935) the diagnosis of hemochromatosis was made in two brothers, with three other brothers and the mother showing some signs of the disease. Also in Butt's and my series of cases one patient, previously reported by Eusterman, had a brother with an enlarged liver and bluish pigmentation; in two other cases in our series a family history of diabetes existed. Beyond this sugges-

[2] To keep the record straight it should be stated that three of the thirty cases in the report of Butt and me previously had been published, one by Allan and Constam, one by Eusterman and one by Dry. Soon after publication of our report another case from the clinic was recorded by Rushton.

tion of inborn constitutional abnormality the cause of the disease is obscure. It does not rest on an abnormal degree of destruction of blood. Nor can it depend on a primary cirrhosis of the liver which would not explain the difference in incidence of age or the extent of the deposits of iron in the liver.[3] The theory of Mallory that hemochromatosis is attributable to chronic poisoning with copper is now generally regarded as untenable, although it is recognized that the copper of the liver is increased in hemocromatosis as well as in portal cirrhosis. Nor does the evidence hold that alcohol plays a significant rôle Sheldon found a history of alcoholism in only 25 per cent of his collected cases, and in Butt's and my series sixteen of the patients were total abstainers, ten rarely took an alcoholic drink and four took only moderate amounts.

Abnormal retention of iron must occur in hemochromatosis, but it is not associated with any demonstrable failure of excretion by the bowel or kidneys Balance experiments by Dry and others have revealed scarcely any deviation from values for intake and output found in normal persons, and thus any retention in excess of the normal must be very small.[4] The total amount of iron in the body of patients with hemochromatosis has been computed by Sheldon as frequently exceeding 40 gm Spread this over a period of five years, a relatively long duration for those manifestations of the disease that have been recognizable clinically in the past, and we arrive at a figure for daily retention of 20 mg A much smaller amount would have been readily detected in the balance

[3] Sheldon has insisted on a sharp distinction between hemochromatosis and hemosiderosis, he used the latter term to denote the deposition of iron pigments that res[illegible]

The view that hemochromatosis is merely an extension of changes always found in portal cirrhosis is untenable It does not explain the difference in sex incidence between the two conditions, nor the extent of the deposits of iron in the liver in hemochromatosis It is true that the liver in portal cirrhosis contains more iron than normal, but "if hemochromatosis were merely an extreme development of this process, one ought to find intermediate cases, whereas these appear to be con spicuously absent The difference in degree is so profound and so sharp that it constitutes a difference in kind" (Sheldon)

[4] Marble and Smith confirmed the findings of the other investigators named, of very small (normal) retention of iron, and agreed with the conclusion that this supports an "inborn error of metabolism" characterized by slow accumulation of iron

experiments referred to. Furthermore, a daily retention of such an amount is an impossibility, since the daily supply of iron in food rarely exceeds 10 mg. Therefore, the onset of the disease must be dated back not five but forty or fifty years from the time a diagnosis is made; such a deduction is consistent with the age incidence of patients with hemochromatosis and gives further support to the suggestion made by Sheldon and Dry—that hemochromatosis represents an inborn error of metabolism expressing itself in an inability of cells to rid themselves of ferrous compounds no longer useful.

PATHOLOGY

In the presence of hemochromatosis, hemosiderin and hemofuchsin, the former predominating, are widely distributed throughout the organs and tissues of the body, with the exception of the brain and nervous system. Very little is found in nervous tissue. The liver usually is enlarged to more than 2,000 gm. It *is rusty red and has a hobnail surface. Microscopically the appearance* is like that of Laënnec's cirrhosis, except for massive accumulation of the pigments. Hemosiderin occurs predominantly within the cells of the liver; less is present in young cells or in areas of regeneration. It is found in the fibrous tissue in areas where hepatic cells have been destroyed. It also is contained in the Kupffer cells, the connective tissue cells, and to a lesser extent, in the walls of blood vessels and bile ducts and in the capsule of the liver. Hemofuchsin, in much smaller amounts, is distributed more diffusely.

The pancreas usually is larger than normal, firmer and of a color similar to that of the liver. Microscopic examination reveals a great increase of fibrous tissue and provides evidence of both degeneration and regeneration of both acinar and insular cells. Pigmentation affects the entire organ in all degrees of severity, *but the islands appear to be injured* as much by the cirrhosis as by the pigmentation, for in many cases islands surrounded by fibrous tissue are grossly degenerated with only a minimal degree of pigmentation.

The changes in *the skin are of special importance from the* standpoint of diagnosis, because skin can be obtained for biopsy The finding of iron in the propria of the sweat glands and about the capillaries of the upper part of the cutis is considered

to be nearly diagnostic of hemochromatosis (Montgomery and O'Leary). Also the normal deposits of melanin in the deeper layers of the epidermis usually are greatly increased. This increase of melanin Hellier attributed to disturbance of adrenal function, the result of deposition of iron and consequent cirrhosis of the adrenal cortices. Sheldon, however, disagreed.[5]

CLINICAL CHARACTERISTICS

The symptoms of hemochromatosis are referable for the most part to bronzing of the skin, associated diabetes mellitus and cirrhosis of the liver When this triad of abnormalities is well developed, the syndrome is definite and nearly unmistakable.

Pigmentation.—A change in the color of the skin is not always present; cases have been reported by Telling in 1921 and by Orr in 1930, in which there was no change. In the series of cases reported by Butt and me from The Mayo Clinic pigmentation was absent in only one case. Although pigmentation itself is rarely cause enough for the patient to consult a physician, usually it is the first symptom to attract attention. It was the first symptom noted in twelve cases in our series; in five cases it was the second

The color of the skin often is described as being between the shade typical of the melanosis of Addison's disease and the slate gray of argyria The pigmentation may appear early or late. In one case in our series it had existed for sixteen years, in ten cases for from one to five years and in one case for less than six months Its distribution usually is general, although exposed portions of the skin are affected most and they alone may reveal the characteristic color. Mucous membranes may be affected In one of our cases the hard palate was pigmented, and in another the gums were involved. This involvement of mucous membranes and in some cases some of the general pigmentation may be attributable to deposits of melanin secondary to involvement of the adrenal glands by hemosiderin, but no direct correlation has ever been demonstrated between the intensity of the pigmentation of the skin and the degree of involvement of the adrenal glands

[5] Auscher and Lapicque considered the nonferrous pigment, hemofuchsin, as closely related to melanin Its high sulfur content is in favor of this view, and its distinction microscopically from melanin certainly is impossible It appears likely, according to Sheldon, that the bronze color of the skin in some cases is mainly attributable to an increase of hemofuchsin, while hemosiderin imparts the bluish metallic nuance frequently seen

Instances have been reported in which after insulin therapy, the pigmentation decreased. This was noted in two of our thirty cases. Sheldon cited Lawrence as suggesting that the fluctuation may depend on a varying amount of glycogen and water in the epidermal cells through which the pigment grains are seen.

Diabetes mellitus.—The diabetes may be mild and readily controlled by dietary measures; in the later stages of the disease, however, it often is severe and in some cases has been unusually

TABLE 9

LABORATORY DATA IN CASES OF HEMOCHROMATOSIS*

	Cases	Results.		
		Average value.	Highest value	Lowest value.
Hemoglobin, per cent	30	74 7	94	46
Erythrocytes, per cu mm of blood	30	3,990,000	4,840,000	2,960,000
Leukocytes, per cu mm of blood	30	6,600	10,200	4,200
Blood sugar, gm per 100 c c	28	0 230	0 440	0 085
Blood urea, mg per 100 c c	*12*	*41 2*	*76*	*24*
Carbon dioxide combining power of plasma, volume per 100 c c	11	54	67	39
Serum bilirubin, mg per 100 c c	16	1 6	4 2	0 5
Blood cholesterol, mg per 100 c c	3	207	264	177
Serum protein, gm per 100 c c	3	6 8	7 8	5 9
Basal metabolic rate, per cent	3	−10	+12	−5
Blood iron (total), mg per 100 c c	1	40†	–	–
Blood iron (total), mg per 100 c c	1	38‡	–	–
Blood iron (total), mg per 100 c c. . . .	1	43‡	–	–

* From Butt and Wilder

† Single determination

‡ Determination made by Sachs and his associates [Sachs, Adolph, Levine, V. C., and Griffith, W O: Blood iron and copper in hemochromatosis Proc. Soc. Exper Biol & Med., 35 332–335 (Nov), 1936]

TABLE 9—(*Continued*)

Fragility of erythrocytes .	2 Normal.
Erythrocyte smears and differential count . .	18 Normal, 15 cases, slight macrocytosis, 3 cases
Van den Bergh reaction	16 Indirect, 14 cases, direct, 2 cases
Dye retention test of hepatic function . .	8 Retention, grade 1, 6 cases, grade 2, 1 case, grade 4, 1 case
Gastric analysis	6 Normal
Dextrose tolerance	5 Normal, 2 cases, diabetic, 3 cases (not previously considered diabetic)
Phenolsulfonphthalein test of renal function	4 Normal
Urine	
Sugar	30 *Present, 24 cases, absent, 6 cases*
Hemosiderin	7 Positive, 2 cases, negative, 5 cases.
Arsenic	2 Positive, 1 case (6 mg in 1,800 c c), negative, 1 case
Tyrosine	1 Positive
Methemoglobin	3 Negative
Sulfmethemoglobin	2 Negative
Copper, iron and lead	3§ Negative
Urobilin, bile and urobilinogen	1 Positive.

§ One case each

refractory to therapy. Eleven patients of Butt's and my series had noted some symptom of diabetes at the onset of the disease; this group and eight additional patients had had symptoms of diabetes for from six months to five years. Only nine patients complained at the time of admission to the clinic of symptoms referable to diabetes, but twenty-six of the thirty patients were demonstrated to have diabetes by laboratory methods Glycosuria was present in twenty-four of the cases, and in four of the six in which glycosuria was not present the level of blood sugar in the morning before breakfast was higher than normal (Table 9).

Asthenia.—Weakness other than what could be explained by the associated diabetes, is a frequent symptom This has been mentioned by several investigators. Asthenia may persist for

In the cases collected by Sheldon, most of the patients had been seen before the discovery of insulin, and the average interval of time between the first medical consultation and death was eighteen and a half months. Of these patients 50 per cent died in diabetic coma. Recent experience indicates, however, that treatment of the complicating diabetes will greatly prolong survival. Death now should have to wait, in most cases, on the effects of the cirrhosis of the liver, such as hepatic failure, hematemesis, infected ascites or carcinoma. Lawrence (1936), after reviewing the course of the disease and duration of life in twelve cases, commented on the improved prognosis as follows· "No one *could yet venture on a prognosis for any particular patient, but it* is clear that death can be postponed and activity made normal for many years. As Sheldon suggests, it is likely that a liver death (cholaemia, cirrhosis and ascites) will replace diabetic coma. As regards the liver, I feel that of all forms of cirrhosis—a hard, very large liver—this is probably the best. Here no violent toxic background is present to kill the liver cells, but a slow mechanical cause, the deposition of an iron excess This gives the liver time to hypertrophy and regenerate enough new cells to maintain full liver function. This can go on adequately for many years, how long no one knows. But no immediately gloomy prognosis is justified if the insulin treatment is successful. I see no reason to tell these patients that they have a fatal disease and think it best, if necessary, to say that their diabetes is complicated by a large liver. The intelligent ones should never hear the words 'bronzed *diabetes' or 'haemochromatosis' when perusal of the older encyclo*paedias must be unnecessarily depressing."

Treatment.—Certainly the most important element in the treatment of hemochromatosis is the correct management of any associated diabetes. *Usually this presents no difficulty.* Later reports from ten of our patients indicated that one was not diabetic, one was controlling the diabetes by dieting, whereas seven required moderate doses of insulin. Only one required an unusually large dose of insulin (180 units per day). In the treatment of diabetic coma in the cases referred to by Sheldon insulin also was normally effective. However, difficulties occasionally arise. Insulin resistance was encountered in one case in The Mayo Clinic (Allan and Constam), in a case of Root and in one

reported by Miller and Heimark. Undue sensitivity to insulin has been met with more frequently; this is attributable, possibly in some cases, to involvement by the hemochromatosis of the anterior lobe of the pituitary body.

It is desirable in hemochromatosis, as in any other condition in which the liver is diffusely diseased, to prescribe a diet relatively rich in carbohydrate and free from meat. Likewise, the administration of concentrates of vitamins A and B_1 are specifically indicated. Other vitamin supplements also may be helpful. Other treatment must be symptomatic

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CHAPTER XXII

ARTERIOSCLEROSIS AND DISEASES OF THE HEART IN DIABETES[1]

The incidence of disease of the arteries in cases of diabetes has been a subject of repeated comment by numerous writers; the consensus is that diabetes hastens the development of arteriosclerosis and speeds its course. My observations of the past have been in accordance with those of Joslin, Nathanson, Blotner, Rabinowitch and others who have come to this belief, but difficulties in interpretation exist which should receive more consideration before these conclusions are accepted with finality. An objection to the evidence is that arteriosclerosis cannot with certainty be excluded by an examination of living persons. The more closely it is looked for, the more frequently it is detected, and possibly the scrutiny of patients for evidence of it, in clinics devoted to the care of diabetes, has been much more intensive than that of persons being examined for life insurance, or of patients in general hospitals with diseases less frequently accused of favoring the development of arteriosclerosis. The same suspicion may be entertained of examinations for arteriosclerosis made at necropsy, namely, that when the body of a diabetic is being examined the pathologist takes more pains to look for arteriosclerosis than he otherwise would take Furthermore it must be recognized that no two pathologists are likely to attribute the same interpretation to lesions of like severity Complete freedom from all abnormality is scarcely ever to be expected, and when more conspicuous lesions are found they may be called moderate sclerosis by one examiner and marked sclerosis by another Thus, even comparisons of statistics obtained at postmortem examinations must be undertaken with caution.

TYPES OF ARTERIOSCLEROSIS

Definitions are necessary in any discussion of arteriosclerosis. Different types of arteriosclerosis are recognized: (1) Arteriolar

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sclerosis is a diffuse lesion involving the arterioles and the finer twigs of the arterial tree, commonly coincident with hypertension. (2) Atheromatosis is a patchy lesion primarily of the intima of the larger arteries. (3) Mönckeberg's sclerosis represents primary necrosis and calcification of the media of arteries with muscular walls. (4) Senile arteriosclerosis is the diffuse fibrosis and degeneration of aging.

The chief pathologic changes of arteriolar sclerosis, as described by Kernohan, Anderson and Keith, are hypertrophy of the media of the arteriole and finer artery, proliferation of the intima of these, and reduction in the ratio of thickness of their walls to diameter of their lumens. The most pronounced and most constant change is the thickening of the media. It is associated with an increase in the number of nuclei and apparently represents true hypertrophy of the muscle. The condition of the intima varies, proliferation may involve both endothelial and subendothelial cells and more or less complete occlusion may occur.

*The lesions of atheromatosis are nodular, with patchy distri*bution in the aorta as well as in the larger, the middle-sized and the smaller arteries with muscular walls. The intima is first affected; it is thickened and contains many star-shaped cells which are filled with lipoid. Later, disintegration and necrosis occur and the fat is distributed in the interstitial tissue. The lumen is encroached upon. Calcification of the plaques of atheroma and fibrosis of the media are irregular, later developments. The roughening of the intima favors the occurrence of thrombosis.

The lesion of Monckeberg's sclerosis also represents a process of necrosis and calcification. It also is patchy, but it primarily affects the media, is not characterized by accumulation of lipoid, and is infrequently complicated by thrombosis. It involves the legs by predilection The fact that various toxic agents such as nicotine and irradiated ergosterol have been shown to cause this type of arterial lesion, and not atheroma, supports the view that Monckeberg's sclerosis differs etiologically from atherosclerosis. However, *Ophüls has written that the two* lesions so frequently occur simultaneously in the same case and in such close topographic relation that one can hardly doubt, in most cases, that they are part of the same process.

Any one or all of these three types of lesion will be associated of necessity with senile arteriosclerosis; that is, with the diffuse changes in arteries which normally accompany the process of aging. They consist of progressive deterioration with splitting of the internal elastic membrane and formation of new fibrous tissue. Late in life extensive fibrosis of the media and even calcification may be found in uncomplicated senile arteriosclerosis, but it must be emphasized that, even in ripe old age, well-marked arteriosclerotic lesions may be absent. This observation, as well as the fact that marked arteriosclerosis develops in many cases before senile changes have set in, shows that old age alone is not the most essential causative factor in most cases. The incidence of arteriosclerosis according to age, in 3000 general necropsies reported by Ophuls, counting only those cases in which the condition was "fairly well marked," was 3.5 per cent for the third decade, 9.25 per cent for the fourth decade, 26 per cent for the fifth decade, 48 per cent for the sixth decade, 78 per cent for the seventh decade and 90 per cent in the eighth decade and beyond.

ARTERIOSCLEROSIS ASSOCIATED WITH DIABETES

Now what do we find in diabetes? In the first place, arteriolar sclerosis, as judged by (1) hypertension, (2) sclerosis of the retinal arteries,[2] and (3) the incidence of arteriosclerotic nephritis is no more common among diabetic patients than among others. The average systolic blood pressures of diabetic patients seen in the George F. Baker Clinic, between 1919 and 1923, was 129 mm of mercury, which is insignificantly higher as compared to Fisher's average figure of 127 mm for 19,339 normal persons of a lower average age. Major, it is true, comparing diabetic patients with other patients in a hospital dispensary, found the blood pressure among the former to be slightly higher, but Wollaeger, in reviewing some of our experience, saw no difference in either systolic or diastolic pressures in a group of 200 patients with diabetes and in 200 nondiabetic patients of the same ages.[3] The patients in his two groups had been examined twice, that is, before and after

[2] Instances of simple diabetic retinitis—punctate hemorrhage and exudation without sclerosis of the retinal arteries—are excluded.

[3] For his controls Wollaeger took otherwise healthy patients who had been referred to the Section on Neurology because of headache. In most of these cases the only clinical diagnosis was migraine.

intervals of five years or more, and the progression of hypertension, in the interval between examinations, was no greater among the diabetic patients than it was among the others.

The eye grounds afford the only opportunity during life to observe lesions of the finer arteries and arterioles of large groups of patients. In the cases reviewed by Wollaeger, examination of the ocular fundi had been made, mostly by Dr. Wagener, before and after intervals of five years or more. The incidence of sclerosis of the retinal arteries was almost identical in the cases of diabetes and in those in which diabetes was not present. No difference was found in the degree of progression of the lesions after intervals of five years or more. The result, as far as comparative incidence of sclerosis of retinal arteries is concerned, is like that reported by Waite and Beetham:

"When they graded the arteries of the retina in four groups and classified them according to grade and age, they came to the *surprising* conclusion that there was no greater amount of sclerosis of the retinal arteries in the diabetics than they observed in the nondiabetic control series."[4]

According to Joslin the incidence of chronic vascular nephritis is much greater among diabetic patients than it is among nondiabetic patients. It was present, he added, in three-fourths of his cases of diabetes in which the patients were more than forty-five years of age. This is entirely contrary to our experience. Nephritis could be diagnosed in only twenty-seven (1 per cent) of a series of 2584 cases of diabetes observed in the years 1935 to 1937 inclusive. Furthermore, Warren, in his intensive study of 484 diabetic necropsies has commented on the small number of deaths (five deaths—1 per cent) that were due to arteriosclerotic nephritis.

Turning now to the question of sclerosis of the larger arteries, we find ourselves dependent on postmortem material, since palpation of peripheral arteries during life and roentgenologic demonstration of calcification give information that is far too unreliable for statistical study. Roentgenologic examination reveals calcification, but does not distinguish arteriosclerosis of the Monckeberg type from atherosclerosis. In the former condition the lumen of the artery is not encroached upon and the

[4] The italics are mine. The quotation is from page 489 of the sixth edition of Joslin's "Treatment of Diabetes," the reference being to the observations of Waite and Beetham with patients from the George F. Baker Clinic.

circulation is but little disturbed, whereas in the atherosclerotic process calcification may be minimal when the patient is suffering from intermittent claudication, gangrene or neuritis. It is the latter process that concerns us most.

Our pathologic material consists of that obtained at necropsy in 139 cases of diabetes in the years 1925 to 1936 inclusive, which was reviewed by Dry and Tessmer, and that obtained at necropsy in fifty-eight cases of diabetes in the years 1919 to 1925 inclusive, which I reviewed in 1926. Unfortunately, permission to examine the brain was obtained too infrequently in our cases to provide significant data, but in 175 cases of diabetes in which necropsy was performed, Root and Sharkey found cerebral arteriosclerosis to be no more frequently a cause of death than it was among nondiabetic patients In our cases of diabetes in which necropsy was performed, as in the cases reported by Warren, the coronary arteries, as might be expected, were severe offenders In the 139 cases of diabetes in which necropsy was performed at The Mayo Clinic in the years 1925 to 1936 inclusive, 130 of the patients were more than forty years of age Coronary occlusion was the cause of death in fifteen (approximately 11 per cent) of the 139 cases In Warren's series of 484 cases in which necropsy was performed, 395 of the patients were more than forty years of age and in eighty-one, or 16 7 per cent, of the 484 cases death was due to coronary occlusion In both series of cases this represents only a small proportion of hearts showing other evidence of coronary occlusion, such as recent or healed infarctions or myocardial fibrosis In the series of Dry and Tessmer such lesions of the heart were encountered in fifty-three additional cases, so that the diagnosis of occlusive coronary disease could be made in sixty-seven cases, or 48 per cent. In Warren's larger series of cases seventy-two fresh and healed infarctions were found in 16 per cent and marked coronary sclerosis with the lumen reduced more than a third—actual occlusion present or not—was found in 124 of 467 cases (28.1 per cent). This incidence for severe forms of coronary sclerosis is significantly greater than has been reported for unselected necropsies On the other hand, the incidence of coronary sclerosis of all grades is not greater. Thus, in 2613 unselected necropsies on patients at The Mayo Clinic who were more than forty years of age, Willius, Smith and Sprague found only 370

instances (14 per cent) in which coronary sclerosis was "unmistakably marked" and sixty-one instances (2.3 per cent) in which coronary sclerosis was "extreme"; however, some degree of coronary sclerosis was noted in 2419, or 92.5 per cent, of the 2613 cases in which the patients were more than forty years of age. The occurrence of arteriosclerotic lesions of the coronary arteries could not be more frequent than this in cases of diabetes.

There is a significantly large proportion of females in cases in which diabetes is associated with severe coronary sclerosis. Combining the series of 130 cases reported by Dry and Tessmer with 440 cases reported by Warren, in which the sex of the patients was reported, severe coronary sclerosis was found in eighty males and fifty-eight females, giving a ratio of 1.4:1. In those, mostly nondiabetic necropsies reviewed by Willius, Smith and Sprague in which the age was over forty years, severe coronary sclerosis occurred in 291 males and eighty-nine females, a ratio of 3.3:1. An explanation for this relatively greater susceptibility of *diabetic women to severe coronary arteriosclerosis is not apparent.*

Occlusion of the arteries of the legs also occurs with unusual frequency in cases of diabetes. In The Mayo Clinic series of 130 necropsies on diabetic patients more than forty years of age, such occlusion sufficient in degree to cause some symptom before death was present in fifty-one cases (39 per cent). Forty of the patients in these cases also had severe sclerosis of the coronary arteries. *Here again the proportion of females was greater than usually is* found among nondiabetic patients who have occlusive vascular disease. The ratio of males to females in a series of 105 cases of diabetes in which there was occlusion of arteries of the legs (fifty-one cases represented in the necropsies previously mentioned; fifty-four additional cases in which the diagnosis was made clinically) was 2.7:1. In a comparable series of nondiabetic patients studied by Hines this ratio was 7.7:1.

Another difference between the series of diabetic patients with occlusive disease of the arteries of the legs and the series of nondiabetic patients studied by Hines was a greater incidence of both gangrene and trophic ulcer. *Such lesions were found in 68 per* cent of the former group and in only 48 per cent of the latter group. This difference probably is accounted for by a greater susceptibility of diabetic tissue to infection.

Root suggested a qualitative difference between the type of arteriosclerosis in the extremities of patients with diabetes and that encountered in other cases. In this I cannot agree. He wrote,

> "In the legs of non-diabetic patients the changes consisting of calcification, necrosis and sclerosis occurring chiefly in the media form the so-called Monckeberg type of arteriosclerosis."

This is true, but the Mönckeberg type of arteriosclerosis also is seen in cases of diabetes and the atheroscleromatous type, which leads more readily to occlusion of the lumen of the arteries, predominates not only in cases of diabetes but also in other cases in which the arteriosclerosis is occlusive. Therefore, I agree with Buerger, who was quoted by Root as writing that the lesions of atherosclerosis of so-called diabetic gangrene "differ in no way from the lesions of the arteries in senile gangrene." Objectionable only in the Buerger statement is the use of the term "senile gangrene." Gangrene of the feet, as observed in nondiabetic patients, is a result, not of the senile type of arteriosclerosis but of occlusive atherosclerosis exactly comparable to that encountered in cases of diabetes.

ETIOLOGY OF ARTERIOSCLEROSIS

That diabetes is not in and of itself a cause of arterial disease is evidenced by the fact, previously cited, that arteriosclerosis of some degree occurs no more frequently than usual in cases of diabetes. Why diabetes should be associated with a greater degree of atherosclerosis is the real problem Possibly infection, to which diabetic patients are predisposed, is responsible, although MacCallum found little evidence in favor of the idea that infection plays much of a part in any arteriosclerosis. Possibly in diabetes fluctuations in the concentration of the blood sugar and periodic development of acidosis lead to intermittent swelling and thereby to lowering of the intercellular substance of the intima, as Warren has suggested However, if this were true we ought to see a correlation between the degree of arteriosclerosis and intensity of diabetes, which is not the case. Everyone who has studied the problem agrees that the mildest diabetes frequently is associated with the more severe grades of atherosclerosis, and vice versa.

Undue emphasis may have been placed by Joslin and his associates on the occurrence of arteriosclerosis in the diabetes of juvenile cases. In Warren's series of 484 necropsies there were fifty-four cases in which the age of the patient was between ten and thirty years and arteriosclerosis was present in twenty-seven (50 per cent) of these cases. However, in the unselected necropsies at The Mayo Clinic, reported by Willius and his associates, some degree of aortic sclerosis was found in 87 per cent of the 519 patients with ages between ten and thirty years, and some degree of coronary sclerosis in 62 per cent.

White, in a study of 104 diabetic children, found that nineteen had calcification of the arteries, demonstrable by roentgen rays. The figure seems large, but no study of nondiabetic children of comparable nutritional status was made or referred to. The children were inmates of a diabetic summer camp; many of them had not been treated before by Dr. White or her associates. Many were grossly undernourished and below normal in stature and development, and this malnutrition rather than the diabetes may be the explanation of their arteriosclerosis. Such cases have not come to our attention, and R. D. Lawrence, of London, in a clinical survey of forty-three diabetic children who had been under treatment with insulin for ten years or more, found, with one exception (showing retinal arteriosclerosis), no vascular disease evidenced by blood pressure, examination of the retinal vessels or roentgenologic examination of the larger vessels. The occurrence of occlusive arterial changes has been confined almost entirely, in our experience and that of Lawrence, to middle-aged and elderly patients who had mild diabetes

Hyperlipemia has been supposed by many writers to occur with unusual frequency in cases of diabetes and to favor the development of arteriosclerosis in such cases. However, Hunt, studying material of the George F. Baker Clinic, found that the most advanced arteriosclerosis occurred in cases in which the average values for plasma cholesterol were low. Also in a very large number of cases in which the concentration of lipoids in the plasma was determined by Osterberg, Rynearson and Kendrick, of The Mayo Clinic, the values among diabetic patients were not unusual as compared to those for patients of comparable ages who were not diabetic.

Another possibility is that nutrition plays a considerable rôle in the production of arteriosclerosis, and that injudicious arrangements of the diet leading to borderline deficiencies in cases of diabetes account for the predisposition to the more severe grades of occlusive vascular disease.[5] I am of the opinion that nutritional excess has received more emphasis than it deserves. Obesity is more likely to lead to arteriolar sclerosis (hypertension) than to atherosclerosis, and thin patients suffer from gangrene as frequently as do those who are overweight.

The foregoing may be summarized by the statement that sclerotic lesions of the arterioles and finer arteries occur with no greater frequency and no greater intensity in cases of diabetes than in other cases, that the frequency of sclerosis of the larger arteries also is not unusual in cases of diabetes, but that the intensity of the process and the incidence of severe grades of atheromatosis and of occlusion of the lumen of the arteries of the heart and legs are significantly greater in diabetics than they are among persons who are not diabetic. Women with diabetes seem to be much more susceptible to severe grades of occlusive lesions than other women, an observation for which no explanation is apparent. While it appears from the evidence submitted by Warren that long duration of diabetes is attended with more progression of atherosclerosis in the heart and legs than can be attributed simply to aging, there seems to be no correlation between the severity of the diabetes and the severity of the atherosclerosis. Finally, it must not be overlooked that patients in very significant numbers, with diabetes of long duration, remain free from clinically detectable evidence of arteriosclerosis, and at necropsy present no more atheroma or other disease of the arteries than is commensurate with the degree of physiologic senile arteriosclerosis to be expected from their ages.[6]

[5] "The span of life can be controlled in rats by diet, often dependent on only slight deviation from the optimum. There is no reasonable doubt that diet influences the duration of man's life. There is much to be learned concerning the effects of a persistently faulty diet which may become detectable only after years or generations" (Weiss and Minot).

[6] In an undetermined number of cases of diabetes with arteriosclerosis the history indicates that disease of the arteries preceded the development of the diabetes. Diabetes among the aged has been recognized as a result of arteriosclerosis ever since the first observations of Hoppe Seyler (1893). This view, cited by Long, is not acceptable to Warren, who found a marked degree of sclerosis of the arteries of the pancreas in only 5 per cent of cases of diabetes in which necropsy was per-

TREATMENT OF ARTERIOSCLEROSIS

The supposed high incidence of arteriosclerosis among diabetic persons, together with the supposed unusual occurrence of elevated values for cholesterol and other lipoids in the plasma in this disease, has induced some clinicians, particularly those who advocate diets high in carbohydrate, to conclude that the arteriosclerosis of diabetes is a result of feeding diets rich in fat. These clinicians have been influenced by the imbibition theory of Virchow, as amplified by the Russians, Anitschkow and Chalatow as well as by Aschoff. However, Duff, of the Department of Pathology of the Johns Hopkins Hospital, has pointed out that the production of arteriosclerosis in rabbits by feeding cholesterol is *not a valid reason for believing that an excess of cholesterol in* the diet plays a part in the cause of the usual arteriosclerosis of man. The lesion produced in the rabbit is not identical anatomically *with that of atherosclerosis as observed in man.* The lesion in the rabbit involves primarily the media of larger arteries. The intima of such arteries is first to be affected by the disease in man. *The lesion in the rabbit is always dependent on hyper*cholesteremia, whereas hypercholesteremia is not observed with any regularity in the arteriosclerosis of man. The lesion in the rabbit is always associated *with deposits of cholesterol in other* organs and tissues; this has no counterpart in the arteriosclerosis of man. A uniform failure has accompanied all attempts to produce arterial *lesions by feeding cholesterol to cats, dogs, foxes and* monkeys, in which the diets and concentration of plasma cholesterol are comparable to those of man. This negative evidence is more important for appl*ication to human conditions than is the* positive evidence obtained from the experience with rabbits. Finally, those pathologic conditions in man which are associated with cholesteremia, *with the one exception, diabetes, are infre-*

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formed Joslin regarded the duration of the diabetes itself as an argument against the opinion, because, as a rule, the older the diabetic becomes, the less severe is his diabetes and the greater is the degree of his arteriosclerosis *However*, another [illegible] metabolism, fac[illegible] Morlock, wh[illegible] [illegible]t, in un- of [illegible] pancreas selected cases of hypertension showed more [illegible] *of* [illegible] was than in any of the other organs exami[illegible] with [illegible] the ar- the earliest change apparent. Later fibr[illegible] occlu- teriolar wall, reduction of the wall to lu[illegible] sion of the lumen.

quently associated with arteriosclerosis. Duff referred to pregnancy, hypothyroidism, obstructive jaundice, certain types of nephritis and lipoid nephrosis. These negative observations on patients with outspoken hypercholesteremia constitute the strongest sort of evidence against the idea that hypercholesteremia acting alone can cause arteriosclerosis. On theoretic grounds it might accelerate the development of arteriosclerotic changes previously initiated by some other agent, but there is little evidence at present, according to Duff, that it plays even this small rôle.

These also were the conclusions of Weiss and Minot. According to them, the evidence which has been brought forward in the attempt to demonstrate the relationship between the cholesterol content of the diet and the development of arteriosclerosis in man is equivocal and therefore not convincing. Indeed, they said that it would hardly influence an opinion not already prejudiced in favor of the idea. Watson and Wharton came to the same conclusions. These authors studied 112 dietary combinations as applied in twenty-seven cases of diabetes and did not observe any significant disturbance of the cholesterol content of the plasma, even with rather extreme variations of the content of fat in the diets.

On the other hand, cases of gross hyperlipemia are seen, some with and more without diabetes, and in such cases restricting the intake of animal fat, as suggested by Schoenheimer and Hrdina, may markedly and consistently lower the concentration not only of cholesterol, but also of lecithin and fatty acids in the plasma. I refer here to cases of "essential hyperlipoidemia" with or without cutaneous xanthomas, in which the values for the several lipoid fractions of the plasma are from two to five times normal. In this disease, evidence of occlusive vascular atheromatosis almost always can be found. It should be emphasized, however, that this is not the arteriosclerosis that ordinarily is encountered among diabetic patients, but an unusual disease occurring among nondiabetic individuals as well as in cases of diabetes; perhaps with equal frequency, and that presumably it depends primarily on some error or abnormality not of metabolism but of the ability of the individual to excrete cholesterol. Possibly transitional forms occur between the atherosclerosis seen in this condition and the forms of arteriosclerosis encountered more commonly,

adjacent blood vessels the circulation is further obstructed and gangrene is promoted The early treatment of abrasions is imperative, but in their treatment the use of antiseptics irritating to the skin must be avoided Diabetic patients leaving our care are advised to consult a physician early for cuts and infections, but several times the physician—even against the protest of the patient—has applied antiseptics such as tincture of iodine or a carbolated salve, with results that were disastrous and easily might have led to legal claims for redress. Dressings saturated with equal parts of saturated aqueous solution of boric acid and 50 per cent grain alcohol, in our experience, are effective and safe, but they should be alternated with dressings of dry sterile gauze Walking on a foot that is infected must be prohibited. Rest is indispensable until healing is complete.[7]

Finally, for all patients with sclerosis of the arteries of the legs, time and effort must be devoted to attempts to improve the peripheral circulation. For this purpose the regular use of contrast baths is recommended, together with massage and passive exercises such as those devised by Buerger.

The following directions are given to diabetic patients in The Mayo Clinic who suffer with occlusive vascular disease:

DIRECTIONS FOR THE CARE OF THE FEET

The patient with diabetes who has poor circulation of blood in the lower extremities is in danger of developing gangrene of the feet He may be able to prevent this complication if he will maintain satisfactory control of his diabetes and heed the following admonitions They are six in number

1 Keep the feet clean, avoid "athlete's foot"

2 Avoid bruises and cuts, giving proper attention to toe nails, corns, stockings and shoes

3 Avoid burning and freezing the skin of the feet, avoid strong antiseptics

4 Avoid constricting the circulation, avoid tobacco

5 Provide rest for injured feet

6 Make use of measures to promote the circulation, contrast baths, massage, exercises

Adherence to these admonitions will obviate the necessity for many an

[7] Reports of six cases in which tetanus complicated moist gangrene were found in the literature by Stoyanoff, who added a seventh The patients all died I have encountered this only once The patient was a farmer and the infection proved fatal [illegible] cur more frequently among [illegible] ng the carelessness of some [illegible] walk on ulcerated feet, and

amputation. Adherence to them will also help to prevent cramps on walking and numbness and pains in the legs at night.

1 KEEP THE FEET CLEAN

Wash the feet daily. Use a nonirritating soap and dry the feet carefully. Avoid rubbing with the towel Blot off the moisture, especially that between the toes. Drawing the towel between the toes or pulling the toes too far apart may cause breaks in the skin.

After the bath gently rub the feet with alcohol, then apply boric acid or other dusting powder. If the skin is abnormally dry, apply lanolin, olive oil or cocoa butter.

Athlete's foot—Watch out for infestation with fungi (athlete's foot) Athlete's foot is to be suspected if tiny blisters are found between the toes, or if cracking and weeping of the skin occur with bad odor and itching Athlete's foot may be acquired in shower baths, on bathing beaches and in hotel bedrooms. Many remedies commonly prescribed for it are too strong for safety when the blood supply to the legs is poor. A reliable and safe treatment is to soak the feet for thirty minutes twice daily in a freshly made 1 8000 solution of potassium permanganate—one 5-grain tablet of potassium permanganate (purchasable at a drugstore) in 2 quarts of warm, not hot, water. The solution stains the skin but is not injurious

2. AVOID BRUISES AND CUTS

Bedroom slippers should be put on before getting out of bed and taken off after getting into bed Walking in bare feet must be strictly avoided because of the danger of stepping on sharp objects or bruising the toes by bumping them.

Toe nails—Toe nails should be cut straight across, not rounded, and should not be shorter than the flesh at the extreme tip of the toe. The corners should not be cut or pulled out Never use a knife; employ nail clippers and a file or emory board, and exercise great pains to avoid cutting the skin and drawing blood. A piece of cotton twisted around the end of an orangewood stick or toothpick and saturated with hydrogen peroxide should be used for cleansing under the nails, not a pointed nail file. A small piece of cotton inserted under the corners of the nails will help to prevent their becoming imbedded in the flesh and will encourage them to grow straight. This cotton must be changed once a week. If the nail bed is painful insert less cotton

Corns—Corns grow from pressure, and if all pressure can be prevented they will disappear Use corn pads (nonmedicated) or cover the corn with adhesive moleskin. If moleskin is used, replace it once a week; omit the covering with moleskin one day each week Above all, wear shoes that neither press nor rub the corn Do not attempt to cut corns or calluses If their trimming becomes a necessity see a chiropodist (accredited Pedicure) Ask your physician to refer you to one who is competent. Remember to tell the chiropodist that you have diabetes, so that he will exercise every precaution to avoid drawing blood or introducing infection

Stockings—Short stockings cause as much foot trouble as ill-fitting shoes There should be some looseness at the toe—room for foot expansion when weight is borne. Pull the stocking out at the toe before putting on the shoe Stockings must be clean. They should be changed once a day and new stock-

ings should be laundered before they are worn Thick darns and seams in stockings are to be avoided

Shoes—Soft leather is to be preferred Shoes should be broad in the toe and straight on the inner border They should fit snugly over the instep so that the foot will not press forward Metal arch supports are undesirable A combination last is best for normal feet This is two widths narrower at the heel than at the ball of the foot Narrow toed shoes must be avoided Crowding the toes leads to ingrown toe nails The heel should be of medium height—not too low The linings must be smooth The counters of new shoes should be softened before the shoes are worn, and new shoes should not be worn more than two hours at a time for the first four or five days

3 AVOID BURNING OR FREEZING THE SKIN OF THE FEET

When the circulation of blood is poor, the skin of the feet is insensitive Thus extremes of temperature may not be recognized Furthermore, the skin of the feet may be injured by temperatures that would not harm other parts of the body Therefore, take great pains to avoid freezing or burning the feet The greatest danger is from hot-water bottles or electric pads These must never be placed below the knee For cold feet at night wear loosely woven woolen stockings in bed Unless special precautions can be taken against overheating, heat lamps or bakers are to be avoided Never place hot water bottles or electric pads below the knee

Test the temperature of the bath water with the elbow or forearm, not with the foot

[illegible]

dressing made of sterile gauze until it dries and flattens of itself Then if it breaks, infection will be less likely Broken blisters are treated with dressings of boric acid and alcohol, as described below

Wear warm wool socks and overshoes in cold weather, and avoid prolonged exposure to cold Should the feet be frozen do not apply heat but warm them by gentle massage

Antiseptics—When treating abrasions of the feet avoid the use of strong antiseptics Tincture of iodine, solution of bichloride of mercury, carbolic acid and medicated salves are dangerous Simple cuts, burns and broken blisters from burns are best treated by applying a sterile gauze dressing kept moist with equal parts of 50 per cent grain alcohol and saturated solution of boric acid Alternate such a dressing with a dry sterile dressing every twelve hours

4 AVOID CONSTRICTING THE CIRCULATION

Circular garters, constricting bandages, overtight shoes and sitting with the legs crossed slow the circulation of blood to the feet Sitting with the legs crossed not only constricts the circulation but also, because of pressure on a superficially placed nerve at the knee, may provoke the development of a neuritis leading to foot drop

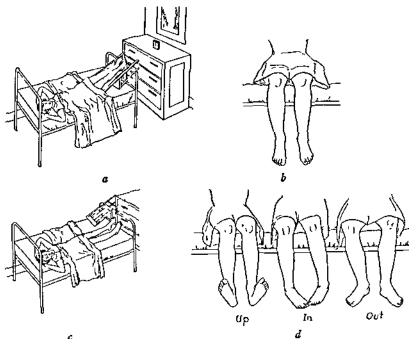
Tobacco—Nicotine slows the stream of blood by causing contraction of the muscular walls of the arteries It is, therefore, advisable to avoid entirely the use of tobacco in any form

5 PROVIDE REST FOR INJURED FEET

Walking on a foot that is bruised, or otherwise injured, delays or prevents recovery. This applies even to minor injuries When only one foot is affected, crutches will provide the necessary rest. When crutches are used they must be well padded, otherwise crutch palsy may develop from the pressure of the crutch at the arm pit. If both feet are affected, the patient must remain in bed unless he can be lifted into a chair. If he sits in a chair, his legs must not hang down Do not step on an injured foot until healing is complete

6 MAKE USE OF MEASURES TO PROMOTE THE CIRCULATION

Contrast baths—Forty minutes devoted once daily to contrast baths and to the massage and exercises to be described, will help greatly to improve the circulation in the legs For the contrast baths two pails are used One is filled with water warmed to 105° F., and the other with water at 50° F *A bath thermometer (procurable at little cost in any drugstore) must be employed to secure these exact temperatures* The feet and lower legs are immersed alternately for one minute in each bath, beginning and ending with



the warm bath and changing from warm to cold and back again five times This takes eleven minutes Add hot water to the warm bath and cold water to the cold bath as necessary to maintain the original temperatures

Massage.—After the contrast bath stroke and knead the feet and legs, beginning at the toes and working upward toward the knees. Use cocoa butter,

lanolin, olive oil or mineral oil as a lubricant. Spend five minutes at this massage

Exercises.—1 Lie flat on the back in bed with the legs elevated for one minute, *a;* then sit on the bed with the legs hanging down for one minute, *b;* then lie flat in bed with the legs horizontal for one minute, *c*. Repeat six times This exercise takes eighteen minutes

2 Stand on toes and heels alternately ten times Sit on a table and swing the legs freely, rotating the feet slowly, as illustrated, *d*. Spend five minutes at this exercise

DISEASE OF THE HEART

Acute rheumatic fever occurs with no unusual frequency in cases of diabetes, and carditis resulting from this or other infectious condition is no more common than otherwise. However, as was explained, occlusive sclerosis of the coronary arteries and the lesions of the myocardium that attend it are found at necropsy in a disproportionately large number of cases A curious fact, in view of this, is the infrequency of cardiac symptoms among diabetic patients In this the report of Root and Sharkey and that of Dry and Tessmer, relating to our experience, are in complete accord Congestive heart failure and dyspnea of cardiac origin are uncommon, and angina pectoris is rarely seen except with occlusive episodes, and then inconstantly. Angina pectoris had occurred in only sixteen of thirty-two cases of coronary thrombosis in the series of necropsies on diabetic patients reported by Root and Sharkey, and the duration of any symptoms in these cases was often only a few months before the occurrence of terminal coronary occlusion In eight of the cases there was no history of pain.[8]

Diagnosis of coronary thrombosis.—Reference has been made to the symptoms of diabetic acidosis, including pain and leukocytosis, which complicate the diagnosis of organic disease of the abdomen, such as appendicitis. Similar diagnostic difficulties may

[8] The very high incidence of hyperglycemia and glycosuria encountered in the acute stage of coronary thrombosis among persons not previously diabetic ought not to be accepted as evidence of diabetes mellitus Raab and Rabinowitz obtained abnormal blood sugar time curves with dextrose in all of twelve cases of coronary occlusion in which the patients were examined within two weeks of their coronary closures, but in only three of nine cases in which the patients were reexamined [illegible]

disease are suffering from diabetes mellitus

be presented when diabetic patients with suspected coronary sclerosis have acidosis, as was illustrated by the following observation in a case reported by Lymburner, Barnes and Rynearson.

The patient, a woman, 52 years old, had been under treatment with diet and insulin for five years. She also had had intermittent retrosternal pain for ten years. It came in attacks usually lasting half an hour, and extended into the left arm. The episode that aroused diagnostic confusion followed an infection of the upper part of the respiratory tract. The patient was admitted to the hospital service in extreme pain. She was dyspneic and her color was ashen. The value for the blood sugar was 0.455 gm. per 100 c.c. The carbon dioxide combining power of the plasma was 11.7 volumes per 100 c.c. Because of anxiety on the score of coronary thrombosis and the supposed danger of overdosage with insulin in cases of coronary disease, treatment was hesitant, with the result that four hours later the carbon dioxide combining power of the plasma had fallen to between 2 and 3 volumes per 100 c.c., and the patient became comatose. Intensive treatment was then started, consciousness returned and except for persistent attacks of precordial pain on exertion the patient fully recovered. During the episode of acidosis the electrocardiogram was abnormal, but not characteristic of coronary thrombosis, and when the acidosis was controlled it returned at once to normal. This fact, combined with the prompt clinical improvement of the patient, was regarded as incompatible with such a serious cardiac insult as acute myocardial infarction.

Treatment of coronary arteriosclerosis.—The treatment of angina pectoris in cases of diabetes does not differ from that customarily employed, except for the control of the associated diabetes. In attacks of coronary thrombosis with accompanying congestive heart failure, resistance to insulin may develop so that large doses of insulin are required. On the other hand, in many cases of arteriosclerotic heart disease the diabetes is mild, demanding the use of relatively small doses of insulin or none at all. There exists a good deal of hesitancy about using insulin in the presence of cardiac disease because of isolated reports of cases in which overdoses have precipitated attacks of angina pectoris. The danger has been exaggerated, at least, no fatalities from this source have occurred in our experience, and only one instance of fatal coronary thrombosis during insulin hypoglycemia has been reported from the George F. Baker Clinic. It is important, nevertheless, to bear the matter in mind and to exercise appropriate precautions. In cases of long standing diabetes the heart may become accustomed to a high concentration of blood sugar and perform less effectively when the concentration is normal. How-

ever, to deprive a cardiac diabetic of insulin when insulin is needed is completely unjustifiable. The cardiac muscle depends on dextrose for maximal efficiency, and in cases of severe diabetes dextrose without insulin is useless.[9]

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CHAPTER XXIII

HYPERINSULINISM: DEFINITION AND DIAGNOSIS*

My motives for introducing the following discussion of hyper insulinism are two: first, to arouse more general awareness of a disease which frequently is curable, and second, to plead against designating as hyperinsulinism conditions associated with low levels of blood sugar in which the low levels of blood sugar are not attributable, with high probability, to an excess of insulin. The symptoms are much the same in hypoglycemia, whatever the cause. Particularly impressive are hunger, weakness, disorientation and striking prompt relief by taking sugar. I hope to make clear, however, that episodes of hypoglycemia do not of themselves establish proof of excessive insulin, and to justify restriction of the term "hyperinsulinism" to those cases in which operation on the pancreas can be expected to effect lasting relief

The disease diabetes was defined in Chapter II as a primary disorder of pancreatic function which involves an insufficient supply of insulin and is characterized most consistently by a persistent tendency to displacement upward of the level of the blood sugar. The disease hyperinsulinism is the clinical opposite of diabetes, being characterized by displacement downward of the level of the blood sugar. The hyperglycemia of diabetes and the hypoglycemia of hyperinsulinism may be corrected by appropriate adjustment of the intake of food, but in both diseases correction accomplished by this means is impermanent. In hypoglycemia as in diabetes a primary disorder of the pancreas is responsible for the disturbance of the level of the blood sugar with an effect which in each instance is continuous.

Hyperglycemia itself is not a disease but a symptom. High values for blood sugar are encountered in many conditions other than diabetes mellitus Similarly hypoglycemia is a symptom which is encountered in a number of abnormal states other than

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those of pancreatic origin; namely, in pathologic conditions of the liver, in cases of insufficient function of the anterior lobe of the pituitary body and irregularly in cases of insufficient function of the adrenal cortices or of the thyroid gland. It also is a symptom of both organic and functional disturbances of the parasympathetic nervous system. A number of writers have expressed the opinion that such nervous types of hypoglycemia represent hyperinsulinism (or dysinsulinism). *With this opinion my colleagues* and I disagree. It is based on the assumption that the pancreas in cases of nervous disorders is intermittently provoked to excessive activity, an assumption unsupported by satisfactory evidence. In my opinion and that of my associates isolated attacks of spontaneous hypoglycemia are not in themselves sufficient evidence to justify a diagnosis of primary disorder of the pancreas, whereas hyperinsulinism, as here defined, is a disease originating in the pancreas.

Another consideration enters into the definition of hyperinsulinism In primary hyperfunction of insular tissue the export of insulin is badly adjusted to the need for insulin Although always excessive for postabsorptive requirements, it may be too small to meet the need for insulin after meals. In consequence the taking of food may elevate the concentration of the blood sugar and even cause glycosuria in the same case in which the level of the blood sugar invariably falls to pathologic levels on prolonged withdrawal of food Actually the export of insulin by a normal pancreas, to compensate for abnormal needs, at times must exceed that encountered in cases of true hyperinsulinism. I can explain by referring to the experiments of Young (see Chapter III), in which, after several weeks, diabetes was produced in previously normal dogs by daily injections of extracts of the anterior lobe of the pituitary gland The earlier injections elevated the values for blood sugar only transiently; that is, if the injections were discontinued, the values fell again to normal. A number of dogs were killed at this early stage of the experiments, that is, before permanent diabetes had been produced, and in them the islands of Langerhans appeared hyperplastic and revealed other signs of increased secretory activity. Under the circumstances of these experiments, until the pancreatic islands had been exhausted, the export of insulin probably was extreme, although it

still was not large enough completely to compensate for the injection of the diabetogenic hormone. Clinical conditions, comparable to the condition Young produced experimentally, are encountered in cases of overactivity of various endocrine antagonists to the islands of Langerhans, and in such cases also we probably are confronted with large exports of insulin. This might be called "compensating hyperinsulinism," but it is not the disease we are concerned with in what we define as hyperinsulinism

DIAGNOSIS

Hyperinsulinism, as so defined, has been established with complete reliability only for patients with hypoglycemia in which operation or necropsy has revealed an adenoma or carcinoma originating in the islands of Langerhans of the pancreas. The number of cases has been small, only twelve were identified in *The Mayo Clinic in twelve years However, in the same period* of twelve years nearly an equal number of patients were operated on without finding tumors, the operation being done because the tendency to downward displacement of the level of blood sugar was persistent and the symptoms presented were indistinguishable from those of the patients with tumors. Under such circumstances, but only then, and always provided no other organic cause for hypoglycemia can be ascertained, is it justifiable, in my opinion, to assume the existence of primary overactivity of nontumorous insular tissue. Such a condition would be analogous to hyperthyroidism in those cases of hyperthyroidism in which tumorous changes are not found in the thyroid gland, analogous, that is, to the condition which is diagnosed as exophthalmic goiter. In exophthalmic goiter diffuse cellular hypertrophy and hyperplasia can be identified in microscopic sections of thyroid tissue. In analogous cases of suspected hyperinsulinism, without tumor, sections of pancreas sometimes, but infrequently, reveal what looks like hypertrophy of the islands of Langerhans. However, estimation of the amount of insular tissue is attended with insuperable difficulties; the ability of the microscopist to recognize pathologic variation in individual insular cells is by no means comparable to his ability to recognize abnormality in the cells of the thyroid gland and in a number of these cases subtotal resection of the pancreas or other comparable procedure has been curative.

The foregoing explains why a degree of uncertainty atten diagnosis in many cases of hyperinsulinism. Before exploring t pancreas a diagnosis can at best only be presumptive, namely, decision as to probabilities. Nevertheless, in all cases of abnorma depression of blood sugar levels, such a decision must be made; because if the evidence for primary overactivity of the pancreas is inadequate, an operation is uncalled for, but otherwise an exploration should be performed. Insular adenomas are prone to become malignant and on this account alone they should be excised. Their removal provides lasting relief, in those cases in which hypoglycemia depends on insulin exported from tumors, and if no tumor can be found, in a case that satisfies the criteria demanded for a diagnosis of hyperinsulinism, surgical methods for reducing the total export of insulin from the pancreas are available.

In arriving at conclusions as to probabilities we are guided largely by the presence or absence of extra-insular conditions known to influence homeostasis of the blood sugar. A review of these reveals (1) a group of disorders of the glycogen depots; (2) a group of abnormalities of various glands of internal secretion other than the pancreas, and (3) a group of disorders of the nervous system, some organic, others functional.

1 Disorders of glycogen depots.—Gross disorders of hepatic parenchyma.—It was pointed out earlier (see p. 6) that almost complete hepatectomy was necessary to provoke hypoglycemia in dogs. In view of this we are not surprised to find that hypoglycemia only occurs as a terminal event in most cases of hepatic disease. This is true in hepatic atrophy of undetermined origin as well as in hepatic atrophy provoked by poisoning with cinchophen, chloroform or phosphorus, in yellow fever, and in cirrhosis and cancer of the liver. Frequently with extensive hepatic nvolvement by cirrhosis or cancer the level of the blood sugar emains undisturbed, but a classical case of very low values for ood sugar and symptoms of hypoglycemia was reported by liott, Nadler and Wolfer.

Selective hepatic disease.—In a few cases of disease of the liver, trary to rule, the glycogen mechanism seems to have been disped without gross interference with other hepatic functions ong such cases are two which were reported from the clinic

by Judd, Kepler and Rynearson In them abdominal operations revealed no abnormality of the pancreas, slight portal cirrhosis and extensive fatty metamorphosis of the liver. The patient in one of these cases previously had been diabetic; also she was known to have taken large doses of sodium iso-amylethyl barbiturate and other sedatives. The patient in the other case had not been diabetic nor had she used drugs In both cases the serum bilirubin was normal in value and evidence of general loss of hepatic function as provided by the bromsulfalein test was slight. Other possible examples of disturbance of the glycogen function of the liver in the absence of comparable loss of other functions are a case of toxic hepatitis reported by Cross and Blackford and three cases of cholangitis reported by Coller and Jackson. In the same category is glycogenosis (von Gierke's disease). Thus far glycogenosis has been recognized only in children. The patient in the first case of the kind to be fully reported (Parnas and Wagner) later became diabetic (Wagner).[1]

Disease of the muscles as a cause of hypoglycemia —In a case of progressive muscular atrophy McCrudden and Sargent found a value of blood sugar of 0.064 gm per 100 c c and noted that administration of carbohydrate was beneficial for the asthenia. Likewise Messini is said to have reported episodes of hypoglycemia in progressive muscular dystrophy However, Rosenow's sys-

[1] An investigation by Seckel of the rate of postmortem hepatic glycogenolysis in two fatal cases, in one of which an insular carcinoma was found, fills a gap in our knowledge When Allan, Power, Robertson and I described the original case of pancreatic tumor with hyperinsulinism, attention was called to a very high *glycogen content in the liver*, and it was suggested that an equally unusual case previously reported by Parnas and Wagner might represent a similar condition The case of Parnas and Wagner, of hepatomegaly, hypoglycemia, ketonuria and re- [illegible]

[illegible] mined, however, either in the original case or in any of the numerous cases of hyperinsulinism which subsequently have been reported, was whether postmortem [illegible]

[illegible] countered in the liver *and muscle in* both cases, but *postmortem hepatic glycogenolysis* was approximately normal or only slightly decreased

An important review of the literature on glycogenosis was published recently by van Creveld, who with Snapper gave the first clinical report of a case of it in 1928

tematic examination of patients with muscular disorders revealed values for blood sugar which, while tending to be low, were all in the normal range.

2. *Abnormality of other glands of internal secretion*.—Pluriglandular dyssynergia.—The category of pluriglandular dyssynergia has been used by some writers as a wastebasket into which to put unusual cases of hypoglycemia when clear-cut evidence was not available to determine which endocrine gland or glands were primarily involved. This never is a satisfactory diagnosis.

Adrenal glands.—Hypofunction of the adrenal cortex in Addison's disease leads less frequently to episodes of hypoglycemia than might be expected Compensatory suppression of the pancreatic islands presumably interferes. However, occasionally in the crisis of Addison's disease and otherwise if patients with this disease are deprived of carbohydrate by long starvation, very low levels for blood sugar have been encountered. Porges was first to call attention to hypoglycemia in Addison's disease, and necropsy in two cases of hypoglycemia reported by Welty revealed tuberculosis of the adrenal glands associated with lymphatism. Rushton, Cragg and Stalker described a case of spontaneous hypoglycemia from The Mayo Clinic attributable to atrophy of the adrenal glands, and cited other instances from the literature.

Greenwald and Eliasberg encountered low values for blood sugar in two cases of severe burns. The patients were children. Subsequent experiments with rabbits revealed that death after burns may result either from initial shock with excitation of the adrenal glands and hyperglycemia, or later from adrenal degeneration and hypoglycemia.

Thymus.—Hyperthymism as a cause of depression of the level of the blood sugar was suggested by MacLean and Sullivan. Messini likewise encountered hypoglycemia in a case in which the thymus was hypertrophic.

Thyroid.—Hypothyroidism is infrequently complicated by depression of the level of blood sugar and symptoms of hypoglycemia are as unusual in myxedema as they are in Addison's disease. However, Janney and Isaacson found moderate lowering of the concentration of blood sugar and obtained flat blood sugar time curves in cases of myxedema, and Goldzieher suspected hypothyroidism in twenty of 112 cases of chronic hypoglycemia. Also

Carmichael described what he called "hyperinsulinism" in association with hypothyroidism [2]

Sex glands.—The sex glands probably contribute unimportantly to the regulation of the level of the blood sugar, and evidence that disturbance of them is ever a cause of hypoglycemia is entirely inadequate. The ovaries are affected by disease of other glands of internal secretion, but that this contributes to the hypoglycemia of hypopituitarism, for instance, is highly improbable. However, Cornell, Le Winn and other authors have commented on the occasional occurrence of hypoglycemia in pregnancy, and Longcope's case of scleroderma possibly should be placed in a category of hypoglycemia attributable to disease of the gonads. The value for the blood sugar in his case was 0.041 gm. per 100 c.c.; symptoms were noted and necropsy revealed bilateral interstitial orchitis and atrophy of only one suprarenal gland.

Pituitary body.—Destruction of the posterior lobe of the pituitary gland does not seem to be attended by low values for blood sugar or symptoms attributable to low levels of blood sugar. On the other hand, sufficient destruction of the anterior lobe results in severe hypoglycemia. Cushing, 1912, reported a value for

[2] [illegible]

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ally was accompanied by a ravenous appetite. The attacks occurred every two to four months, and in October, 1938, such an attack was associated with marked nervousness, tremor, episodes of dizziness, insomnia and waves of heat and sweating. The patient's weight by then had fallen from 165 to 135 pounds (74.8 to 61.2 kg.). Determinations of the basal metabolic rate were made but they were inconclusive, and the fasting value of blood sugar had been found to be 0.060 gm. per 100 c.c. A diet high in carbohydrate had been prescribed with frequent feedings. Other symptoms included marked dyspnea, palpitation and a great loss of strength and endurance.

On examination at The Mayo Clinic tremor and a moist skin were noted but the thyroid gland was not conspicuously enlarged. The systolic blood pressure was 146 mm. of mercury, the diastolic 90 and the pulse rate was 96 beats per minute. The fasting blood sugar was 0.083 gm. per 100 c.c.

solution was prescribed and proved somewhat beneficial. Subsequently subtotal thyroidectomy was performed and 10 gm. of thyroid tissue was removed. The definite characteristics of exophthalmic goiter, parenchymatous hypertrophy and hyperplasia were noted in the thyroid tissue removed. Gain in weight and disappearance of all preoperative symptoms followed the operation.

blood sugar of 0.039 gm. per 100 c.c. in a case of chromophobe adenoma of the pituitary, and comparable observations have since been made by others. In some cases of chromophobe adenoma of the pituitary gland with low levels for blood sugar, as in one reported by Cushing, symptoms referable to the hypoglycemia have been absent; in others severe convulsive episodes with loss of consciousness have occurred. The literature on this subject has been reviewed by J. Wilder, who himself reported important observations. From a study conducted at The Mayo Clinic by Foley extensive destruction of the anterior lobe of the pituitary gland appears necessary before any disturbance of the regulation of the blood sugar can be detected. Foley examined the patients in twenty-six successive cases of chromophobe tumor of the pituitary gland, and found only one who had pathologic values for blood sugar. In this instance the values were as low as 0.030 gm. per 100 c.c. In the other cases, although other signs of hypopituitarism were present in the majority, the lowest postabsorptive value was 0.072 gm. per 100 c.c.[3]

Low renal threshold for dextrose.—In renal dextrosuria when the renal threshold is greatly depressed (see Chapter II) restriction of the intake of carbohydrate may result in hypoglycemia. Phlorhizin poisoning, which lowers the renal threshold for dextrose, has been observed clinically only by Mandel and Lusk, who gave phlorhizin to a criminal. However, Fischler called attention to the symptoms observed in dogs poisoned with phlorhizin. His designation "glycoprive intoxication" placed emphasis on the etiologic significance of the associated hypoglycemia.

3. Disorders of the nervous system.—Organic disease of the brain.—Sporadic instances of hypoglycemia have been encountered in schizophrenia, melancholia, hebephrenia and other psychoses, and by Rathery, Derot and Sterne in cases of subdural hemorrhage. Severe hypoglycemia was found by Birnbaum and Wood

[3] Cases of diabetes mellitus have been reported by Lyall and Innes and MacCallum in which amelioration of the diabetes accompanied the development of chromophobe tumor of the pituitary gland. An excellent review of the literature [illegible] and Ehrmann. They [illegible] ne curve can be taken [illegible] of the pituitary body [illegible] quently obtained with perfectly normal subjects, and Foley in his study at The Mayo Clinic obtained low flat curves (mean height 0.117 gm. per 100 c.c.) in only nineteen of twenty-six cases of chromophobe tumor. In the other seven the curves had a high peak.

to accompany the seizures of general paralysis. The observation suggests that other diffuse lesions involving the brain stem may be responsible for some cases of hypoglycemia, lesions, for instance, that might result from previous severe attacks of hypoglycemia induced by injections of insulin or from other causes It has occurred to me that such lesions might explain convulsive episodes irregularly associated with very low levels of blood sugar observed in certain cases of diabetes in which the level of the blood sugar is unusually variable.

The explanation of hypoglycemia in cases of organic disease of the brain is that irritation of centers in the brain stem disturbs a nervous regulation of the blood sugar However, the usual result of irritation of the base of the brain is hyperglycemia, not hypoglycemia.

Epilepsy.—A number of writers, among them Harris (December, 1933), have expressed the view that hypoglycemia may be of etiologic significance in idiopathic epilepsy, at least in the provocation of attacks. Holstrom, however, considered the lowered levels of blood sugar found at the time of attacks to be an effect of the attack on the vegetative nervous system The clinical similarity between some attacks of severe hypoglycemia caused by true hyperinsulinism and the attack of idiopathic epilepsy has frequently led to the mistake of diagnosing epilepsy in cases of hypo glycemia This has been emphasized by Harris (Feb 4, 1933).

Functional disease of the nervous system.—In many cases of symptomatic hypoglycemia the patient is found to be afflicted with one or another of the various neuroses I recently reviewed the associated diagnoses in those cases from The Mayo Clinic in which a diagnosis of hypoglycemia had been recorded The cases numbered 138. In thirty-three of them the associated diagnosis was hyperinsulinism, in six it was hepatic disease, in one necropsy revealed adrenal atrophy, in one the pituitary gland was destroyed by a chromophobe tumor, in eight the renal threshold for dextrose was depressed, and in two clear evidence existed of organic disease of the brain. When the number of the cases, in which the hypoglycemia seemed to depend on primary disorders of glands of internal secretion, was subtracted from the original number, 138, it left eighty-seven cases, and of the eighty-seven an associated diagnosis of some type of neurosis had been made in seventy-two.

Among the seventy-two there were two cases in which migraine was named, six of duodenal ulcer associated with some form of psychoneurosis, six of hysteria, eight of idiopathic epilepsy, and fifty in which the physician had recorded chronic nervous exhaustion or psychoneurosis.

Hypoglycemia associated with neurosis is what I referred to in the introduction of this chapter as a nervous type of hypoglycemia The patient, as a rule, is an emotionally unstable person. He complains of hunger and weakness before meals, and may report that he has fainted on occasion. If so, he has recovered consciousness in a few minutes without treatment. He often complains of low or high pulse rates, irregular respiration and immoderate perspiration, but these symptoms usually are not greater in his episodes of hunger and weakness than at other times. He may be hungry and weak at mealtime, but his hunger and weakness disappear in an hour or two if the meal is not taken. Especially notable is an absence of any trouble at night, and when determinations of blood sugar are made after the night's fast the values are not abnormally low.

In this nervous type of hypoglycemia the symptoms and the low levels of blood sugar usually are related more to the taking of food than to withdrawal of food. The episodes appear two, three or four hours after meals, and particularly after the ingestion of carbohydrates, whereas long periods of fasting are not productive of symptoms. If dextrose is given to such patients, as in the standard dextrose tolerance test, the hypoglycemic phase of the blood sugar time curve is often exaggerated, with very low values at the second, third or fourth hour. At this time the patient may experience symptoms, but he will recover without treatment and can fast afterward for twenty or more hours without the return of symptoms, and with a reasonably satisfactory level of blood sugar at the end of the fast.

The failure of the blood sugar values to remain at pathologically low levels during fasting is evidence that the pancreas is not continously secreting insulin in such cases. Experiments with protamine-zinc insulin have revealed that a very small continuous supply of insulin suffices to cause pathologic levels of blood sugar in fasting subjects. The assumption that the pancreas, in cases of this type, is intermittently provoked to excessive activity

by nervous stimulation is unsupported by evidence, and it is more probable that the hypoglycemia encountered in them is a result of direct action of the nerves on the glycogen mechanism of the liver.

The neurologic picture in these cases of nervous hypoglycemia is that of instability of the autonomic nervous system with predominance, as a rule, of features of vagus irritation In many of the cases of spontaneous hypoglycemia which I placed in this group, the associated diagnosis was vagotonia

Effort hypoglycemia.—Patients with nervous hypoglycemia seem less able than others to withstand effectively the strain placed on the homeostasis of the blood sugar by exercise. Exercise if sufficiently strenuous may produce severe hypoglycemia even in trained healthy athletes. This was demonstrated by Levine and his associates and by Jokl. Since knowledge of it has become general, athletes have taken to eating sugar before competitive exertions Not all runners in a marathon race are affected alike. Even before it was learned that eating sugar would prevent collapse some were able to complete the race with a normal level of blood sugar. The type of person who is most likely to fail in this respect is the type with instability of the vegetative nervous system.[4]

Lactation hypoglycemia.—The sparing effect of lactation on the insulin requirement of diabetic women received comment before (see Chapter XIV). Stenstrom and others have observed depression of the level of the blood sugar in normal nursing women and at times this was associated with symptoms. The same condition is observed in highly bred cows, in which it goes by the name of milk fever, although there is no fever (Harding).[5]

[4] [illegible] rence among patients who have unstable vegetative nervous systems.

[5] Although the explanation of lactation hypoglycemia, usually given, is an abnormal abundance of milk, a more likely one, I suggest, is that the persons affected are individuals with irritable autonomic nerves An etiologically dissimilar milk sickness was attributed by Bulger and his associates to poisoning of cattle with the plant, white snakeroot (Eupatorium urticaefolium) The cattle acquire immunity, but transmit the poison through their milk to their calves and to human consumers The effects frequently are lethal The disease was much more common formerly, in pioneer days in some localities it caused appalling loss of human

DIAGNOSTIC CRITERIA

With a good history and careful examination the extra-insular forms of hypoglycemia which depend on disease of organs other than the pancreas usually can be identified. There remain the cases of nervous origin, and distinguishing the hypoglycemia encountered in them from the hypoglycemia of hyperinsulinism is the really difficult task. In making this differentiation Whipple has been guided by three criteria. When they are met, his diagnosis is hyperinsulinism and the patient is accepted for operation. They are (1) a postabsorptive blood sugar value of less than 0.050 gm. per 100 c.c., (2) symptomatic attacks of hypoglycemia which occur only when the patient is fasting, and (3) relief of such attacks by administration of sugar, preferably intravenously, and without the patient's knowledge of what is injected. By adherence to these criteria of operability and employing an operative technic for mobilizing the duodenum so that the posterior aspect of the head of the pancreas can be brought into view, Whipple has discovered tumors of the islands of Langerhans in fifteen out of eighteen cases in which operation was performed.

The criteria we have used in The Mayo Clinic for selecting cases in which tumors ought to be looked for surgically differ only in minor particulars from those of Whipple. They are (1) normal *health and evidence of stability of the autonomic nervous system* prior to the first episode of hypoglycemia, (2) postabsorptive levels of blood sugar of less than 0.060 gm. per 100 c.c., and (3) intolerance for fasting.

Previous health.—In all of the cases of insular tumor that have been encountered in The Mayo Clinic, and in most of those reported in the literature, the patient enjoyed normal health up to the time of the first episode of hypoglycemia. This first episode, in all but a few cases, occurred not many months before the

life The symptoms are attributable to extremely low levels of the blood sugar This type of hypoglycemia should more properly be referred to under the category hypoglycemia of hepatic origin, since the parenchyma of the internal organs of affected individuals are found at death to be grossly degenerated. Carl Sandburg, in his "Abraham Lincoln, the Prairie Years," tells how Lincoln's mother, Nancy Hanks Lincoln and Tom and Betsy Sparrow were taken down with the "milk sick." "The 'milk sick' took more people in that neighborhood [at Little Pigeon Creek in Indiana] the same year, and Tom Lincoln [Lincoln's father] whipsawed planks for more coffins One settler lost four milch cows and eleven calves The nearest doctor for people or cattle was thirty-five miles away. The wilderness is careless"

patient came under medical observation, subsequent attacks followed with increasing frequency. A year or two after the onset of symptoms nearly all of the patients required feedings at night and in the daytime between meals, or attacks occurred with such frequency as to be incapacitating. Previous health and this type of course are encountered in cases of hepatic hypoglycemia and in those of severe hypofunction of the anterior lobe of the pituitary gland. They are not characteristic of the hypoglycemia of nervous origin. Nothing can be told in the attack, but if between attacks the patient is emotionally well adjusted, and if the history indicates that prior to the first occurrence of attacks he was free from neurotic complaints, the suspicion of primary disease of the pancreas is strengthened. On the other hand, evidence of emotional instability or the existence of other stigmata of autonomic instability (low blood pressure, sweating, low or high pulse rates, irregular respiration and irritable bowels) some years before the first attack speaks for instability of the nervous elements of the blood sugar regulating mechanism and weighs against a diagnosis of hyperinsulinism.

Low postabsorptive level of blood sugar.—In all forms of hypoglycemia the level of the blood sugar in a symptomatic attack may be very low, although in the hypoglycemia of nervous origin it is likely not to be as low as in true hyperinsulinism. Much more important diagnostically is a low value of blood sugar after the night's fast. In cases of true hyperinsulinism this value always has been lower than 0.060 gm per 100 c c, whereas in cases of hypoglycemia of nervous origin the blood sugar level after the night's fast is usually more than 0.070 gm. per 100 c c. (Fig. 13).

Intolerance for fasting (the fast test).—The first attacks of hypoglycemia, early in the course of hyperinsulinism often are precipitated by some unusual exertion, and at this stage differentiation of hyperinsulinism from effort hypoglycemia of nervous origin presents great difficulty. As a rule, however, first attacks in hyperinsulinism occur in the early morning before breakfast, which is very suggestive because in cases of nervous hypoglycemia *attacks almost never occur at this time. With true hyperinsulinism* food must be taken at least with usual regularity and if a meal is missed, an attack is likely to follow. With hypoglycemia of nervous origin fasting, as has been said, is tolerated well. In a

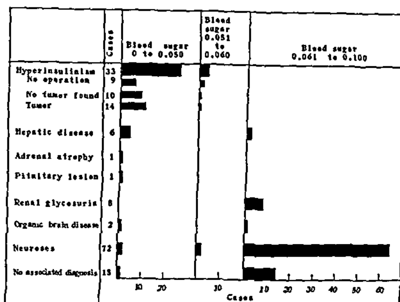


Fig 13 —Values for postabsorptive blood sugar in cases of spontaneous hyp glycemia at The Mayo Clinic.*

occurred in the year following its regular use. Values for postabsorptive blood suga ranged from 0 046 to 0 075 gm per 100 cc. At the conclusion of a fast test c twenty four hours the value was 0 078

The second case was that of an unmarried young woman who in 1934 receive the diagnosis of constitutional inadequacy, hysteria and anorexia nervosa Th values of postabsorptive blood sugar were 0 064 and 0 067 gm per 100 cc At th

0 085, but after a twenty four hour fast a value of 0 085 was obtained Blood was obtained for examination at the time of a number of episodes of disorientation, double vision and headache, but in no case was the value for sugar in these attacks below physiologic limits, and recovery from the attacks occurred every time spontaneously Two months later an operation was performed elsewhere for acute appendicitis The surgeon explored the pancreas and found nothing abnormal

The fourth case was that of a child four years of age with capricious appetite, poor eating habits and irritability The body weight was 28½ pounds (12 9 kg) ... 0 050 ... value ... a boy

five years of age, had always been well until one morning on which he awakened asked for water, refused breakfast and slept again until 10 00 o'clock. He then

suspected case in which the level of the blood sugar is above a diagnostic level we subject the patient to a supervised "fast test." In this test all food is withheld for a period of thirty hours, unless before the end of such a period characteristic symptoms have been provoked and a characteristically low value for blood sugar has been determined. Water is not withheld, but tea, coffee and drugs are not given and smoking is not allowed The patient is encouraged to be up and to exercise mildly, but not unusually. He must remain in the hospital and arrangements are made to determine the concentration of blood sugar immediately on the appearance of symptoms or otherwise at intervals of six hours When symptoms appear, they are allowed to develop to the point of loss of orientation, and then but not until then, or at least not unless a value for blood sugar of 0 040 gm. per 100 c c. or less has been obtained, is sugar administered as a restorative.

The fast test is not intended for application in cases of evident insufficiency of the liver, adrenal or pituitary glands Such disease can be recognized by other means The test is for use when no extrapancreatic cause of hypoglycemia is apparent, or when convulsive states such as epilepsy are to be distinguished from hyperinsulinism. The chief value of the test is in distinguishing between hypoglycemia dependent on instability of the vegetative nervous system and that attributable to primary disease of the pancreas. In a case of nervous instability the patient tolerates the fast with minimal inconvenience, and the level of the blood sugar is usually as high at the end of the period of thirty hours as it was at the beginning, whereas in hyperinsulinism the development of symptoms almost always necessitates the termination of the fast long before the end of twenty-four hours, and the blood sugar then is lower than 0 050 gm. per 100 c c.

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took more water but no food and played with other children Before the midday meal he began to grit his teeth, "froth at the mouth" and perspire Examined by a physician half an hour later he was found unconscious, with flaccid muscles, slow, regular respirations, but normal color The breath smelled of acetone The boy was taken to the hospital where he was catheterized and blood was drawn The urine was not abnormal, but the value for the blood sugar was 0 026 gm per 100 c c. Administration of dextrose intravenously was followed by prompt return to consciousness. Subsequently blood sugar values obtained before breakfast and in the course of a dextrose tolerance test all were normal. Three years have passed since this episode and the child has remained perfectly well and free from any evidence of hypoglycemia

Less reliable diagnostic criteria.—In our experience the dextrose tolerance test has been of little value in the diagnosis of hyperinsulinism. The hypoglycemic phase following that of hyperglycemia in a standard dextrose tolerance test varies widely with different healthy subjects, or with the same subject on different days. Furthermore, to judge from what we have seen as well as from the literature, all types of blood sugar time curves may be encountered in cases in which an operation later has revealed an insular tumor (Fig. 14).

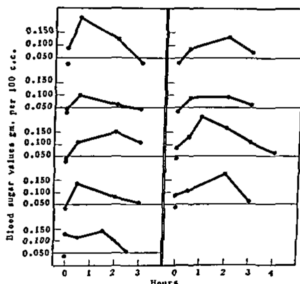


Fig 14—Blood sugar time curves in hyperinsulinism (tumor found).

The elevating effect of an injection of epinephrine on the level of the blood sugar is unreliable diagnostically. In many cases of established hyperinsulinism it has been slight or absent; in others it has been present or even marked Injection of insulin also has been of negligible diagnostic help.

The mere fact that symptoms are relieved by giving sugar should be interpreted with the greatest of caution. Allan correctly demanded that the level of blood sugar actually be demonstrated to be low at the exact time the symptoms are present before permitting a conclusion that any symptom is at all related to the level of the blood sugar.

ERRONEOUS DIAGNOSIS IN SPONTANEOUS HYPOGLYCEMIA

While it is important to avoid a diagnosis of hyperinsulinism when hypoglycemia is caused by extra-insular abnormalities, it is equally important not to mistake the symptoms of hypoglycemia for those of other diseases. Such a mistake not only leads to failure to suspect hyperinsulinism when hyperinsulinism exists, but it also leads to failure to recognize the numerous cases of hypoglycemia of nervous origin which can be treated satisfactorily by modification of the diet as proposed by Harris

Kepler and Moersch found the early diagnoses, made for the most part elsewhere than at The Mayo Clinic, in twenty-one cases of severe spontaneous hypoglycemia to be as follows: attacks of unconsciousness with or without convulsive features in fifteen cases, acute confusional state in eight, stupor or coma in four, spells of weakness in four, alcoholic intoxication in three, vertigo or dizziness in three, tumor of the brain in three, hysteric spells in two, acute delirium or mania in two, spells of amnesia in two, epilepsy (as the only diagnosis) in two, and lethargy (encephalitis) in one. The physicians for the most part appreciated that they were dealing with conditions that did not conform to any of the more usual clinical syndromes

Among the more common disorders that may be confuse[d] with spontaneous hypoglycemia are, duodenal ulcer and gastr[o]intestinal neurosis, because of the occurrence of spells of fatig[ue] which are associated with hunger or mental apathy and are [re]lieved by ingestion of food; intoxication from alcohol or dru[gs]; idiopathic or jacksonian epilepsy, hysteria; fugues; somn[am]bulism, narcolepsy; psychotic conditions associated with deliri[um], mania or depression; states of stupor or coma, such as occur in [di]abetes or uremia, organic disease of the brain, such as tu[mor], encephalitis, paresis, apoplexy, and other diseases in which m[ental] or nervous abnormalities occur To avoid confusion with the physician needs only to become hypoglycemia conscious

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CHAPTER XXIV

HYPERINSULINISM. INCIDENCE AND PATHOLOGY

INCIDENCE

An experience of ten years with spontaneous (pathologic) hypoglycemia was reviewed in 1937 by Kepler and Moersch. At that time attention was called by them to existing conflict of opinion on the matter of incidence. According to a number of authors who include under hyperinsulinism conditions which my colleagues and I now regard as states of functional hypoglycemia of nervous origin, one might infer that hyperinsulinism was almost as common as diabetes. On the other hand, among the first 18,000 patients admitted to a large hospital of the Veteran's Administration there was only one case in which hyperinsulinism was recognized, and to the date of the review of Kepler and Moersch less than thirty patients had been treated at The Mayo Clinic for disabling spontaneous hypoglycemia. It has been our opinion that pathologic hypoglycemia, regardless of its etiology, is a relatively rare condition. We recognize, however, that because of its deceptive manifestation it undoubtedly occurs in milder forms with a somewhat greater frequency than our experience would indicate.[1]

[1] The incidence of cases of hypoglycemia dependent on instability of the vegetative (parasympathetic) nervous system may be more numerous in the Southern states than in the North. Harris, writing in 1932, had recorded the fasting value for blood sugar of 1,497 nondiabetic patients. Sixty-seven of them had hypoglycemia of varying degrees, that is, the concentration of blood sugar of forty-six was between 0.070 and 0.079 gm. per 100 c.c., of seventeen it was between 0.060 and 0.069 and of four, 0.056, 0.050, 0.047 and 0.045 respectively. Nearly all of the seventeen patients with values between 0.060 and 0.069 had symptoms of hypoglycemia, but in only five were they sufficiently severe to justify the diagnosis by Harris of hyperinsulinism.

One of my assistants, Dr. T. B. Tooke, has made the interesting suggestion that habitual drinking of Coca Cola, which is so very prevalent in the Southern states, may explain the greater frequency of occurrence of periodic hypoglycemia in the patients of Southern physicians. Coca Cola is a beverage providing from 18 to 27 gm. of sugar to an average 6 ounce portion (180 c.c.). Consumed as it usually is on an empty stomach its effect is like that of the dose of dextrose given in a sugar tolerance test, for it causes a quickly developing hyperglycemia followed by hypoglycemia. Furthermore, this effect of a drink of Coca Cola may be intensified by the caffeine it contains.

Among the cases of hypoglycemia reviewed by Kepler and Moersch were twenty-one in which the final diagnosis was hyperinsulinism.[2] In nine of these the conclusion as to hyperinsulinism was established by the finding at operation or necropsy of a tumor of the islands of Langerhans. In three an exploratory operation was refused by the patient, and in nine an operation was performed but no tumor could be demonstrated. The failure on the part of a surgeon to visualize a tumor does not exclude the existence of such a tumor. In a number of instances a second or third operation or a subsequent necropsy has revealed a lesion previously obscure

Of the twenty-one patients with a diagnosis of hyperinsulinism, fifteen were men and six were women. The ages ranged from eighteen to fifty-seven years. The average age at the time of diagnosis was forty-three years; the average duration of symptoms was three and one-half years. Symptoms had been present for as long as ten years in three cases in which operations were performed. An insular tumor was found in one of them; no tumor was revealed in the other two. The postabsorptive value for the blood sugar, or the value for the blood sugar at a time when symptoms of hypoglycemia were manifest, ranged from 0.028 to 0 046 gm. per 100 c.c. Another review of a series of ninety-nine cases collected from American and English literature is contained in a paper of Malamud and Grosh. The etiologic factor in twenty-seven of them was an insular neoplasm; in four hypertrophy or hyperplasia of the islands had been reported; in nine a subtotal pancreatectomy had been performed, the pancreatic tissue appearing normal, and in fifty-nine the diagnosis was functional hyperinsulinism [3]

[2] *A later count (1939)* of all cases in The Mayo Clinic with a clinical diagnosis of hyperinsulinism is given in Chapter XXV

[3] In their ninety-nine cases collected from the English literature, Malamud and Grosh compared the type of dextrose tolerance curve *with the etiologic factor* [illegible] ore [illegible] ases [illegible] nal [illegible] per- [illegible] insulinism a high type of curve was found A better correlation was [illegible]ned when the shape *of the curves was compared to* the severity of symptoms When cases were classified arbitrarily according to severity or mildness, a high type of curve almost always accompanied severe symptoms and low type of curve, mild symptoms

INSULAR TUMORS

Soon after Banting and his associates, among them the Toronto clinicians Campbell and Fletcher, recognized that overdoses of insulin produced hypoglycemia and that characteristic symptoms accompanied hypoglycemia, a number of writers described the occurrence of similar symptoms in states of spontaneous hypoglycemia. Among such reports was one by Gibson and Larimer, who made the comment: "It seems likely that hypoglycemic symptoms, not artificially produced, are a definite clinical entity" Symptoms developed immediately after the third hour of a dextrose tolerance test in the cases reported by Gibson and Larimer; the values for blood sugar at the time were 0.040 and 0.045 gm per 100 c.c. respectively. Questioned as to the occurrence previously of similar attacks, one of the patients stated that she had been so affected.

A few months later a report by Seale Harris (1924) appeared in which the suggestion was made that spontaneous hypoglycemia may depend on an overproduction of insulin. Harris attributed the low values for blood sugar found in the five cases in his report to hyperinsulinism, and suggested that the condition represented "a disease entity with definite symptoms, *i e*, those described as being due to hypoglycemia." The conclusion of Harris was based on symptomatology alone, but anatomic support for the conception was supplied in 1927 by my colleagues and me (Wilder, Allan, Power and Robertson) We described a case of metastatic insular tumor which Warren later credited with establishing "a firm foundation for the new clinical entity hyperinsulinism" and providing "the final proof of the insulin origin of diabetes" In the original report of this case special emphasis was placed: (1) on the demonstration that cancer cells removed by metastasis from the parent cells were capable of elaborating the hormone (insulin) characteristic of the parent cells, (2) on the evidence of unregulated activity in the export of insulin from the tumorous island cells, whereby insulin reached the blood in excess of current needs, and (3) on the firmness with which glycogen was bound by the liver, as evidenced by the failure of epinephrine or pituitrin to prevent hypoglycemia. A summary of the case and of the clinical investigation reported with it follows:

Among the cases of hypoglycemia reviewed by Kepler and Moersch were twenty-one in which the final diagnosis was hyperinsulinism.[2] In nine of these the conclusion as to hyperinsulinism was established by the finding at operation or necropsy of a tumor of the islands of Langerhans. In three an exploratory operation was refused by the patient, and in nine an operation was performed but no tumor could be demonstrated. The failure on the part of a surgeon to visualize a tumor does not exclude the existence of such a tumor. In a number of instances a second or third operation or a subsequent necropsy has revealed a lesion previously obscure.

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[b] In their ninety-nine cases collected from the English literature, Malamud and Grosh compared the type of dextrose tolerance curve with the etiologic factor. Although a high type of curve, denoting a high concentration of blood sugar, predominated in the cases of neoplasm of the islands of Langerhans, in five such cases the curve was of a low type. In two instances of a high type of curve a normal pancreas was seen at operation. Furthermore, in six cases of functional hyperinsulinism a high type of curve was found. A better correlation was obtained when the shape of the curves was compared to the severity of symptoms. When cases were classified arbitrarily according to severity or mildness, a high type of curve almost always accompanied severe symptoms and low type of curve, mild symptoms.

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Case 1—The patient was a physician from South Dakota. His age in 1926 was forty years. Epigastric distress simulating that of peptic ulcer had led to a gastro-enterostomy in 1919. Renal calculi had provoked colic in 1924. The family history contained an account of the death of a paternal cousin with symptoms that led to a clinical diagnosis of myasthenia, but which resembled those we today would attribute to attacks of hypoglycemia.

The patient had been examined in The Mayo Clinic in February, 1922, and again in January, 1925. The urine at the time of the renal colic in 1924 had contained sugar, but at our examination in 1925 the fasting value for the blood sugar was normal.

The symptoms prompting the visit to the clinic in 1926 had been present for eighteen months. They began as attacks of faintness and weakness, associated with numbness of the tongue and lips. As time passed these episodes occurred more frequently and were accompanied by greater weakness, profuse perspiration and trembling. They came when meals were delayed or if unusual exertion was undertaken, and the patient himself learned that he could prevent them by eating between meals.

In November, 1925, a more severe attack resulted in collapse. The patient had been operating later than usual and, being overtaken by weariness, was soon mentally confused and fell in a stupor. Attendants thought he had lost consciousness, but he was able to swallow an eggnog which an assistant gave him, and in a few minutes had completely revived. The similarity of this phenomenon to an insulin reaction led the patient and his associates to the belief that he was affected with an endogenous oversupply of insulin, and from this time on food was eaten at more frequent, regular intervals. Six months later, preliminary to a clinical examination elsewhere, a short period of fasting resulted in a coma which lasted two hours. Resuscitation was effected by an intravenous injection of dextrose. As time passed, the tendency to hypoglycemia increased, so that the interval between the patient's taking food had to be decreased and it became necessary for his wife to watch when the patient slept and to put candy into his mouth at the first sign of unusual behavior.

The physical examination revealed nothing unusual other than moderate overweight. The systolic blood pressure measured in millimeters of mercury was 110, the diastolic 60. The pulse rate was 90 beats per minute. The abdomen was soft but not tender, the edge of the liver was firm and rounded. It could just be palpated below the costal margin.

Clinical investigations—Our studies included observations on the re-
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injection of dextrose with the Woodyatt pump, an estimate was made of the hourly requirement for dextrose. It amounted to 25 gm per hour (0.34 gm per kilogram of body weight per hour).

The respiratory quotient after the test meal of 100 gm of dextrose rose above unity to 1.06, which is unusual in normal human subjects but is seen when insulin is administered simultaneously with a dose of dextrose or fructose. After a meal of 100 gm of fructose the respiratory quotient rose to 1.08. In a dextrose tolerance test the concentration of blood sugar reached the diabetic value of 0.218 gm per 100 c.c. at the end of half an hour, and at the two hour point was 0.214 gm per 100 c.c. However, at the end of

three hours the concentration of blood sugar had fallen to 0 031 gm per 100 c.c.

On one occasion 1 mg of epinephrine was administered when the patient was beginning to manifest symptoms of hypoglycemia and the blood sugar level was 0 031 gm per 100 c.c The symptoms were not affected and sugar had to be given four minutes later to prevent collapse. On another occasion 1 mg of epinephrine was injected at a time when the patient felt well and the value for the blood sugar was 0 056 gm per 100 c c. This produced an unusually intense circulatory response but did not interrupt or delay the fall of the blood sugar, which twenty-four minutes later had reached 0 025.

Pituitrin was equally ineffective in delaying the fall of the blood sugar or the development of symptoms of hypoglycemia

No evidence could be obtained of disturbance of hepatic function, either from the value for serum bilirubin or by the administration of the dye, phenoltetrachlorphthalein The nitrogen partitions of the blood and urine were normal and when the amino-acid, alanine, was administered in a dose of 25 gm., and later in a dose of 40 gm, its deaminization apparently proceeded normally.

No food other than carbohydrate would prevent the development of hypoglycemia, and the response to withholding carbohydrate was as follows

Sugar was withheld after a mixed noon meal The patient remained in bed under constant observation The systolic blood pressure was 110 mm of mercury and the diastolic 60 The first symptoms appeared three hours and twenty minutes after the meal, when the level of blood sugar had fallen to 0 055 gm per 100 c c.; the patient experienced a sense of apprehension and depression with vague paresthesias In four hours the level of the blood sugar had reached 0 036 gm per 100 c c; the face twitched and speech was incoherent At this time the systolic blood pressure was elevated to [illegible]

minutes after administration of 15 gm of dextrose by mouth rational conversation was resumed Retrograde amnesia followed each episode of hypoglycemia.

A surgical exploration finally was performed by Dr W J Mayo The pancreas as described by him was large, hard and nodular, with the exception of the head, which seemed fairly normal Metastases could be felt in the liver A small bit of liver was removed and immediately analyzed for glycogen by Dr M H Power using Pfluger's method The result, as glycogen, was 3 49 per cent.

For sixty-three hours after the operation dextrose was given continuously by vein with the Woodyatt pump At first a rate of injection of only 7 gm per hour maintained the blood sugar, but after sixteen hours the requirement increased to 25 gm an hour, and on the resumption of oral feedings as much as 1,000 gm of dextrose a day became necessary

Findings at necropsy—The patient died a month after the operation Necropsy was begun in less than three hours The pancreas weighed 120 gm. Its head and the greater part of its body appeared normal The tail was enlarged and contained numerous yellow rounded nodules (Fig 15).

ranging in diameter from a few millimeters to 1 3 cm The regional lymph nodes were irregularly enlarged. The liver was very large, weighing 3 392 gm It contained five tumorous nodules with diameters from a few millimeters to 6 cm (Fig 16) The glycogen content of the liver, as determined by Pfluger's method, was 8 25 per cent.

Microscopic examination revealed the normal tissue of the tail of the pancreas to be replaced extensively by masses of tumor cells embedded in dense connective tissue and arranged in irregular strands (Fig 17) The cells closely resembled those of the normal islands of Langerhans in the surrounding tissue. The cytoplasm was slightly basophilic; the nuclei were large and contained nucleoli and irregularly distributed basophilic granules In certain regions necrosis was extensive.

Masses of tumor cells were found in an adjacent lymph node. The mass of the liver was not abnormal in appearance. The nodules in the liver were composed of cancer cells resembling those of the tumor of the pancreas They were arranged in close association with blood-filled sinuses (Fig 18) Mitotic figures were noted.

Extraction of insulin —Parallel extractions for insulin were made from pieces of the noncarcinomatous portion of the liver and from a carcinomatous metastatic nodule in the liver. The insulin activity of the former was nil, that of the latter represented an insulin content for the tumor tissue of approximately 40 units for each 100 gm.

Soon after the report of this case, announcements of similar observations were made by Thalhimer and Murphy, McClenahan and Norris, and others, and by 1933 I was able to find in the literature sixteen instances of island tumors; in fourteen symptoms of hypoglycemia were associated (Wilder, 1933). In nine of these cases a correct diagnosis had permitted the operative removal of isolated tumors and the cure of the disease. In some instances multiple nodules of tumor had been found in the pancreas. In some cases minor evidences of malignancy had been noted. Subsequently other cases were reported in which metastasis had involved distant organs. Bru and Slye and Wells described a metastatic island cancer in the dog.[4] Another clinical case in which insulin could be extracted from the metastatic lesion in the liver by Power is described later (see p 387). A case of Bickel, Mozer and Junet is of interest because in it pre-existing diabetes gave place to hyperinsulinism, and at necropsy carcinoma of the

[4] The necropsy of the animal with metastatic tumor of the islands of Langerhans, described by Bru, is of interest, because of its bearing on the theory of [illegible] fundamental elements of the [illegible] primary cancer of the [illegible] en typical island cells [illegible] affected the liver and [illegible] tion of any transition to acinar cells



Fig 15 — Pancreas with distal half split lengthwise The tumor is in the last quarter and the cyst is surrounded by tumor substance



Fig 16 — Liver with tumor nodules in superior portion of right lobe

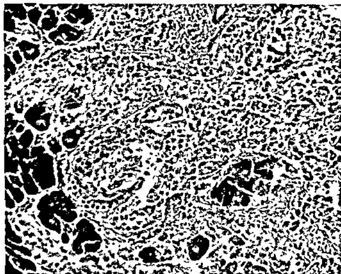


Fig 17—Pancreas and tumor cells (× 120)

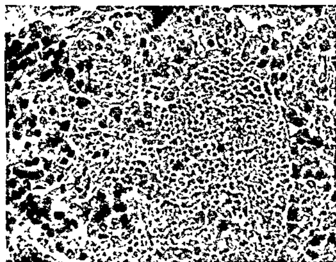


Fig 18—Nodule in liver, carcinomatous masses closely associated with blood sinuses (× 250)

islands of Langerhans was found with metastasis to the liver. The studies of O'Leary and Womack and those of Whipple and Frantz have added greatly to our knowledge of island tumors Laidlaw has proposed for them the name "nesidioblastoma."

Cytology of insular tumors—Bensley of Chicago is pre-eminent as an authority on the cytology of the pancreas His assistance was solicited for identifying the type of cell in the carcinomatous tissue removed from the pancreas and liver in our first case of insular tumor. He also examined tissue from the case described by Thalhimer and Murphy, finding "striking similarity between the cells of this tumor and those of the Wilder-Robertson tumor." In both cases the cells appeared to him "packed with granules that were less sharply defined and not so discrete as in normal island tissues freshly preserved by suitable fixing agents" Sometime later very fresh surgical material was obtained for him by Dr A. O. Fisher. Its treatment with neutral red showed many cells of the tumor packed with granules and giving the impression that the tumor was composed of island cells. Fixation of this with Bensley-Zenker fluid revealed that the fine granules when stained with Bensley's or Bowie's stains were unusual, leading to the conclusion that the tumor was composed of a modified beta type of island cell (Carr and associates, 1931).

In his report on fresh tissue removed from another case by Dr. E. A. Graham, Bensley wrote "The cytologic study of this and of the preceding tumor, and of the one reported by Robinson [Howland and associates, 1929], indicates that in this case the tumor is not one composed of normal island cells but, on the contrary, one composed of cells which, while having a considerable resemblance to island cells, yet differ from them in important details. These differences consist of the production of a granular *secretion antecedent, which differs in important details from the* normal content of the island cells, and in the presence in these cells of a chromophil substance, which is unusual to island cells and is found in the normal pancreas only in the acinus cells.

"The normal pancreas, as is well known, contains a very considerable excess of island tissue and yet ordinarily does not yield to the general circulation an excess of insulin. The fact that a tumor of such meager proportions could produce the symptoms of insulin shock and yet not be responsive as the normal

islands are to the mechanisms that ordinarily regulate the export of insulin from the pancreas, is possibly to be found in the fact that the lesion under discussion is an abnormal cell type which, to be sure, resembles island cells but is not identical with them.

"Some doubt exists in my mind as to whether this tumor should be regarded as adenoma or carcinoma. The failure to form a definite capsule and the inclusion of normal pancreatic elements in the tumor itself seem to favor the latter diagnosis."

In correspondence with Rynearson, Bensley wrote: "I wish very much that I could say something which would stop the clinical people from calling these tumors associated with hypoglycemia 'beta cell tumors.' The one thing that is conspicuous in all that I have examined so far is that they are actually neoplastic cells . . . probably producing insulin or some related substance."

INSULAR HYPERPLASIA

In a number of cases in which surgical exploration has been attempted and insular tumors have not been found, diffuse insular hyperplasia has been present. Phillips reported the following case:

> A man fifty-six years of age was found in the street unconscious The next morning, coma persisting and the value for blood sugar being 0.045 gm. per 100 c.c., 55 gm of dextrose was injected. The amount may have been inadequate because consciousness was not restored On the third day the blood sugar value was 0.025 gm per 100 c.c. and the patient died At necropsy the pancreas was normal in gross appearance but revealed abnormally large islands The average size of these islands was 328 by 242 microns, as compared to normal measurements of 157 by 146 microns given by MacCallum Complicating glomerulonephritis may have contributed to the final outcome, but this could not have caused hypoglycemia and nothing else of importance was found

Large islands have been described in other cases. The condition may represent diffuse insular hyperplasia comparable to the hyperplasia of the thyroid in exophthalmic goiter. However, the difficulty of estimating the size of the islands and the great variability observed in islands of the pancreas of patients presenting no evidence of insular overfunction make it hazardous to place much reliance on the size of islands.[5]

Insular hyperplasia of infants of diabetic women.—The frequency with which hypoglycemia is encountered among the otherwise normal infants of women with diabetes was mentioned in my discussion of pregnancy complicating diabetes (Chapter XIV). The fact that the insulin requirement of the diabetic mother frequently diminishes during the last trimester of a pregnancy is readily explained if we may assume that the maternal tissue is supplied with insulin by the fetal pancreas. The experiments of Carlson and Ginsberg, later confirmed by Cuthbert, Ivy, Isaacs and Gray, support the assumption, and the finding at necropsy of insular hyperplasia in infants born of diabetic women further justifies the conclusion that a maternal demand for insulin in diabetic women is met by the fetal pancreas. The result of this at the birth of the infant is hyperinsulinism for the infant; its pancreas is tuned up to provide a larger supply of insulin than is required for its own tissues. The case which first called my attention to this type of hyperinsulinism was that of Gray and Feemster.[6] The patient, a multipara, had had diabetes for fifteen years. She gave birth to a child that died a short time after delivery with symptoms of hypoglycemia. The child's pancreas contained hyperplastic insular tissue in an amount estimated to be many times normal. The average dimensions of the islands were 290 by 212 microns and the larger ones measured 394 by 335 microns

Gordon examined the pancreas of four babies born of diabetic mothers, and noted hypertrophy of the islands and vacuolization of hepatic cells in all of them. He likewise repeated the experiment of Carlson, in which pregnant female dogs were depancreatized The puppies died shortly after they were born, and hyper-

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with the increasing incidence of diabetes mellitus is also to be thought of Possibly the effect of the various factors, diet, climate, and so forth, which were considered in my discussion of pathogenesis of diabetes (see Chapter III) is reflected by these larger islands If so, we not only may be facing the prospect of more diabetes but also in the [illegible]

[illegible]

and I have suggested in explanation of the peculiar distribution geographically of hyperparathyroidism

[6] Reported earlier, but little appreciated at the time, was the similar finding of Dubreuil and Anderodias

plasia of the islands and vacuolization of the cells of the liver were found. Ehrich observed many islands measuring from 500 to 600 microns in diameter in the pancreas of the child of a diabetic woman, and Warren, in 1938, found hyperplasia of the islands in two-thirds of nine infants of diabetic women. Also individual cells were enlarged.[7]

LESIONS OF THE LIVER, KIDNEYS AND BRAIN IN HYPERINSULINISM

Deaths from overdoses of insulin as well as fatal cases of spontaneous hyperinsulinism have yielded opportunities for very complete pathologic descriptions. Reviews of them can be found in Warren's monograph, as well as in the paper of Malamud and Grosh.

Tests of hepatic function in cases of pathologic spontaneous hypoglycemia have not given abnormal responses, except in two cases from The Mayo Clinic in which hepatitis was present at biopsy. Adequate or large amounts of glycogen have been found when looked for, except by Terbrüggen and Rienhoff and Lewis, who examined for glycogen only by the histologic method. In a case of Malamud and Grosh hepatic tissue removed for analysis ten minutes after death contained only 0.05 per cent of glycogen. *In most instances the appearance of the liver has been normal*

As a rule the kidneys have been normal. Of peculiar interest were the large amounts of glycogen in the epithelium of the convoluted tubules in the case which was described in detail (see p 370). Such a finding is characteristic of diabetes mellitus, but in diabetes renal glycogen disappears when insulin is administered.

The brain is the site of greatest abnormality in fatal cases of hyperinsulinism. Capillary injection, scattered hemorrhages, perivascular *infiltration of round cells, atrophy of the cortex with* degeneration of ganglion cells and swelling of the glia and axis cylinders have variously been found at necropsy. Similar changes have been seen in experimental animals. According to Stief and Tokay both diffuse and focal types of parenchymatous degeneration can be produced in the cortex of the brain and basal ganglia, the severity of the changes being directly proportional to the

[7] Hyperplastic islands of Langerhans associated with hypoglycemia have been reported *in an infant* of a normal woman by Hartmann and Jaudon

doses of insulin and the duration of its administration. Grayzel entertained the belief that the severity of such changes depended on the frequency and intensity of accompanying convulsions. In a case reported very fully by Malamud and Grosh the changes in the neurons of the cortex were predominantly "Nissl's acute swelling" The cells and their dendrites were swollen, there was chromatolysis of the tigroid substance and the cytoplasm was homogeneous and pale The nuclei were swollen. The axis cylinders were reduced in number and frequently were fragmented and swollen Distinct changes were found in the caudate nucleus and in the putamen and thalamus, especially in the left pulvinar, in which the neurons were greatly reduced in number and the microglia and macroglia had undergone proliferation. Only diffuse swelling of the neurons were observed in the hypothalamus, cerebellum, brain stem and cervical spinal cord.

Moersch and Kernohan studied the brains of two patients who died at The Mayo Clinic in attacks of hypoglycemia. They observed petechial hemorrhages in the pons but the outstanding abnormality in both cases was degeneration of nerve cells.

Various hypotheses have been offered to explain the injury sustained by the central nervous system in hypoglycemia. None of them are entirely satisfactory. Malamud and Grosh interpreted the diffuse degeneration of the brain as a direct toxic effect of insulin. However, in cases of resistance to insulin tremendous doses have been given without provoking cerebral symptoms of any kind. Ischemia and hydremia have been incriminated, but the evidence for doing so is not satisfactory. Of undoubted significance is the fact that the nerve cell depends primarily on dextrose for its nutrition, and that deprivation of dextrose results in its starvation. From the episodic course of clinical hyperinsulinism and the complete recovery usually observed between attacks of hypoglycemia, one must conclude that the changes in the brain usually are reversible. However, after severe or more prolonged attacks permanent mental disorders may develop, as reported by Malamud and Grosh. In cases like the one that follows degenerative cerebral lesions are certainly to be expected.

Cerebral injury from induced hypoglycemia, report of case—A boy eight years of age was brought to The Mayo Clinic December 9, 1938 The child had seemed to be normal until the age of five years when polyuria and poly-

lipsia developed. After several days the urine was tested and sugar was found. The next day coma developed and he was sent to a hospital elsewhere. A diet was prescribed and insulin was used, after which he remained in good condition until January, 1937. An overdose of insulin in January, 1937, precipitated violent tetanic convulsions. On admission to a hospital elsewhere, appropriate treatment was instituted but unconsciousness persisted for six weeks. The value for the blood sugar at the time of admission was 0.030 gm. per 100 c.c. The concentration of serum calcium was 6.8 mg. per 100 c.c. Following this episode the patient's mental condition never returned to normal. Repeated examinations of spinal fluid gave negative results, and other examinations were without diagnostic significance.

The mental condition had not improved when we saw the patient and amounted practically to complete idiocy. The shape, size and percussion of the head were normal. No abnormalities could be seen in the eye grounds, and roentgenograms of the head revealed no abnormality. The patellar reflexes were hyperactive, but Babinski reflexes were not obtained. Also there were no localizing signs to suggest a space-occupying lesion. A flocculation test for syphilis gave negative results.

Our clinical diagnosis was idiocy secondary to a degenerative lesion of the brain from overdosage from insulin.*

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CHAPTER XXV

HYPERINSULINISM· SYMPTOMS AND COURSE

The disease, hyperinsulinism, runs a chronic but episodic course from the beginning to the end, and if the patient learns or is instructed to use sugar to prevent and treat the symptoms, the occurrence of dangerous attacks of hypoglycemia may be postponed for years. However, a patient who had metastatic insular carcinoma (case 5 in this chapter[1]) lived only nine months after the first symptoms, and the eighteen-year-old girl (case 4, see p. 387) who was perfectly healthy until early in August, 1933, died in a state of coma and convulsions the following December 15.

ONSET AND EARLY SYMPTOMS

The first symptoms of the disease usually are insidious. In the initial attack hypoglycemic crisis leading to complete loss of consciousness may occur without previous warning, but as a rule, mild episodes precede the development of more serious trouble. These come if a meal is delayed, in the early morning hours before breakfast, or after some unusual physical exertion. In one case encountered at The Mayo Clinic (case 10) spells of weakness with hunger, sweating, nervousness and thick speech occurred at infrequent intervals for thirty-eight years before consciousness was lost in an attack. In our first case of hyperinsulinism episodic weakness with perspiration and trembling was noted for six months before an attack caused collapse. In case 3 in this chapter the first episodes consisting only of drowsiness gave place to serious attacks in six weeks When the patient in case 3 first noticed symptoms she was dieting to reduce The first attacks in two cases reported by Winans likewise were noted by patients who were dieting.

Many of the early symptoms resemble those encountered in neurasthenia, hysteria or narcolepsy. They may consist only of

[1] Cases reported in this chapter are numbered beginning with case 1. Case 1 is reported in detail in Chapter XXIV In previous chapters, although various illustrative cases are reported, there was no need to number them.

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these states into another in the same attack. With apathy negativistic behavior is common, or if the patient is irritated, the apathy may give place to restlessness or even mania. Disorientation exists for time, place and persons. The patient behaves as if he were intoxicated with alcohol. Hallucinations occur, impulsions are observed. Retrograde amnesia is always a prominent feature of all severe attacks. The patient will carry on a conversation with fair coherence, or drive an automobile through a crowded street, and have no recollection of it afterward. A structural iron worker in such an attack descended without injury from the tenth floor of the steel frame of a building under construction, but had no recollection of how he reached the ground A curious fixity of expression is seen, resembling that of Parkinson's disease. An outstanding feature is an automatism with the ear marks of somnambulism.

Affections of motor nerves.—Motor disorders are important, but usually they are less conspicuous than the disturbances of behavior. Convulsions occur as an epileptiform crisis, but in most cases they are not severe and are tonic rather than clonic Diplopia, inarticulate speech, rigidity of limited groups of muscles, moderate general hypertonia, aphasia and agraphia are frequently seen The early symptom, fatigue, sometimes becomes so marked that it seems to the patient as if his feet were glued to the floor. The patient, early in an attack, may still be aware that he ought to take sugar, but does not have the strength to move an arm to do so One patient in one attack, which occurred in his office, tried to telephone his wife but could not hold the receiver Such fatigue probably is of psychic origin, but true paralysis also is encountered Individual cranial or peripheral nerves may be involved as monoplegias, and hemiplegia or paraplegia is seen infrequently In my experience bilateral positive Babinski reflexes have almost always been demonstrable in severe attacks, and the tendon reflexes generally have been increased. The motor abnormalities usually disappear with recovery from an attack, but sometimes they persist for a short period after consciousness is regained, and in rare instances a permanent residue has resulted.[2]

[2] The explanation for residual sensory motor and psychic phenomena after attacks of severe hypoglycemia is to be found in the damage done to the brain Mention of this is made in Chapter XXIV

drowsiness, as in case 3, of inability to attend closely to conversation or to engage in an intellectual pursuit, such as reading. One of our diabetic children receiving insulin (induced hyperinsulinism) stood high in all classes at school except one, which came in the late afternoon, at a time when the level of his blood sugar was lowest. A light lunch was given before this hour and the low grades immediately improved. The frequently intense sense of hunger led Harris to call hypoglycemia, the "hunger disease."

The patients as a rule are not overweight before the onset of symptoms, although many of them gain weight later as a result of symptomatic hunger and attempts to prevent attacks by eating frequent meals. For the most part good health has been enjoyed until the first symptoms of hypoglycemia appear. A history of gastro-intestinal disturbance has been given frequently, as was noted by Gammon and Tenery, and this often has been coincident with the onset of symptoms of hypoglycemia. Two of our patients had undergone operation for supposed peptic ulcer but no ulcer was found. Gallstones had been removed in one case (case 11) but benefit did not result.

Later in the course, attacks of slightly greater severity are characterized by weakness, sweating, tremor, tachycardia and feelings of anxiety. A sensation of chilling also may be complained of. These symptoms, many of them vasomotor in type, cannot be distinguished from those of functional hypoglycemia based on imbalance of the vegetative nervous system. More significant of true hyperinsulinism is the occurrence of signs of involvement of the brain: headache, paresthesia, diplopia, dysarthria, disorientation and particularly amnesia. These evidences of cerebral abnormality are of more significance diagnostically than actual loss of consciousness since loss of consciousness occurs in hysteria and epilepsy or may represent simple syncope.

NEUROLOGIC ABNORMALITIES

Mental disturbances.—Abnormal mental states are encountered in early mild attacks and as prodromes of the later episodes of greater severity. They consist of restlessness, irritability, delirium or even mania, or of the reverse of these, apathy, automatic behavior or stupor. The patient may pass from one of

these states into another in the same attack. With apathy negativistic behavior is common, or if the patient is irritated, the apathy may give place to restlessness or even mania Disorientation exists for time, place and persons. The patient behaves as if he were intoxicated with alcohol. Hallucinations occur, impulsions are observed. Retrograde amnesia is always a prominent feature of all severe attacks. The patient will carry on a conversation with fair coherence, or drive an automobile through a crowded street, and have no recollection of it afterward. A structural iron worker in such an attack descended without injury from the tenth floor of the steel frame of a building under construction, but had no recollection of how he reached the ground. A curious fixity of expression is seen, resembling that of Parkinson's disease. An outstanding feature is an automatism with the ear marks of somnambulism.

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Hypoglycemic coma.—In many severe attacks the stage of coma is reached without much prodromal warning and before restorative treatment can be given. The coma may be mild so that the patient can be roused by a pin prick or pinching, or so deep that sensibility is lost completely. The tendon reflexes remain active, the pulse remains strong, the blood pressure is normal or elevated, and the color of the skin and mucous membranes remains healthy. In the stage of subcoma the respirations are frequently noisy and stertorous; in deeper coma they often are so shallow that the patient scarcely seems to breathe. A weak pulse, diminished blood pressure and cyanosis are terminal events and should be regarded as criteria of extreme gravity.

The value for the blood sugar in the severe attacks of hypoglycemia of patients with established hyperinsulinism invariably has been very low—almost always less than 0.050 gm. per 100 c.c. and frequently less than 0.030. Between attacks values of all degrees can be found, depending on the time which has elapsed since the last ingestion of food and the character of the food. The values may be high for an hour or two after taking of food even in the range of diabetic values.

Restorative effect of sugar.—The restorative effect of sugar is even more dramatic in attacks of hypoglycemia of spontaneous origin than in those induced by overdoses of injected insulin. If dextrose is given intravenously, a patient who is maniacal can be calmed almost instantly and one who is deeply comatose restored to consciousness in a minute or two. If the sugar is given by mouth, it also usually is promptly effective. To some extent, however, the degree of immediate restoration depends on the severity and duration of the attack and after prolonged attacks, headache, some spasticity or more rarely monoplegia or an ab

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One of the earliest reports of examination of the brain in a case of spontaneous hypoglycemia was that of Terbruggen, in a case described by Frank. Necropsy revealed multiple adenomas of the pancreas, hyperemia of the brain, multiple hemorrhages of the brain, and acute fatty changes of the ganglion cells with loss of Nissl bodies. The patient, an unmarried woman about thirty years of age, had suffered for a year from episodic fatigue and abnormal behavior. When dressing in the morning she would try to pull her stockings over her head and leave the house before she was dressed. One morning she was found unconscious in bed and was taken to a hospital, where twenty-four hours later the value for the blood sugar was found to be less than 0.040 gm. per 100 c.c. Dextrose was administered but consciousness was never restored. Death came three days later from bronchopneumonia.

normal mental state may persist In one case of spontaneous hypoglycemia for which Judd, Kepler and Rynearson suggested an hepatic cause, the patient failed to regain consciousness for a week, although the concentration of blood sugar was raised to hyperglycemic levels. In a number of cases in which hypoglycemia has been induced by injection of insulin residual disturbances have been noted. Klein and his associates, Simons and Ligterink of the mental asylum in Apeldorn, Holland described a case in which permanent idiocy followed overdosage of insulin The reflexes of the lower extremities were diminished during the state of shock, but later returned. Epileptic convulsive seizures of the jacksonian type developed without further hypoglycemia Another example of idiocy following overdosage of insulin was referred to previously (see p 377)[3]

Continuous hypoglycemia.—In untreated early cases of hyperinsulinism, as in cases of diabetes in which doses of insulin are only moderately excessive, a state of continuous hypoglycemia may develop which differs in important particulars from the episodic attacks usually seen under these circumstances. More trouble has been encountered in this respect in cases of diabetes with protamine-zinc insulin than with unmodified insulin The level of the blood sugar under these circumstances is low but not at critical values; attacks do not occur but there are continuous manifestations, such as headache, asthenia and paresthesia. A few patients receiving protamine-zinc insulin have complained of sensory neuritis. Mild mental disturbances may develop, the patient being apathetic, abnormally irritable or quarrelsome Diabetic patients have been considered psychopathic when a lowering of the dose of insulin would remedy their condition, and patients suffering from unrecognized spontaneous hypoglycemia have been committed to institutions with a diagnosis of schizophrenia or other mental disease.

[3] Sherrill and MacKay with injections of protamine zinc insulin produced hypoglycemia of thirty hours' duration in rats and for from three to five days in dogs When dextrose was administered as a restorative, some of the animals died Those that survived had residual sensory and motor disturbances These consisted of disorganization of the emotional status, muscular incoordination, spasticity and paralysis One dog recovered entirely except for hemiplegia on the right side Another dog, that before the period of hypoglycemia had been amiable and docile, later greeted anyone who approached him with a snarl

Hypoglycemic coma.—In many severe attacks the stage of coma is reached without much prodromal warning and before restorative treatment can be given. The coma may be mild so that the patient can be roused by a pin prick or pinching, or so deep that sensibility is lost completely. The tendon reflexes remain active, the pulse remains strong, the blood pressure is normal or elevated, and the color of the skin and mucous membranes remains healthy. In the stage of subcoma the respirations are frequently noisy and stertorous, in deeper coma they often are so shallow that the patient scarcely seems to breathe. A weak pulse, diminished blood pressure and cyanosis are terminal events and should be regarded as criteria of extreme gravity.

The value for the blood sugar in the severe attacks of hypoglycemia of patients with established hyperinsulinism invariably has been very low—almost always less than 0.050 gm. per 100 c.c. and frequently less than 0.030. Between attacks values of all degrees can be found, depending on the time which has elapsed since the last ingestion of food and the character of the food. The values may be high for an hour or two after taking of food even in the range of diabetic values.

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REPORTS OF CASES OF HYPERINSULINISM

A better understanding of the variability of the course and protean nature of the symptoms of spontaneous hyperinsulinism may be gained from the following abstracts of the records of cases seen in The Mayo Clinic between 1927 and 1939, in which the osis of hyperinsulinism was established by the discovery operation of an insular tumor of the pancreas.

Case 1.—This case was described by Allan, Power, Robertson and me and has been reviewed in Chapter XXIV.

Case 2—This case was reported by Allan, Rixford, Freeman and Brown as case 2 and by Judd, Allan and Rynearson as case 6.

The patient, a laborer, aged forty-five years had had symptoms for four years They developed when he was at work and because of drunken behavior he was discharged In severe attacks he had convulsions In one such attack he was stuporous for twenty-five hours and then recovered spontaneously. He learned to drink milk to ward off the episodes

Several abnormal values for the blood sugar were obtained. Sometimes when concentration was as low as 0 040 gm. per 100 c.c., the patient seemed normal, but if it dropped to 0 030 he became stuporous Otherwise no abnormalities were detected.

At operation an insular adenoma, measuring 3 cm in diameter, was found and removed Postoperative pneumonia and a pancreatic fistula delayed recovery, but the ultimate result was satisfactory Two years later the patient reported that he had obtained complete relief.

Case 3.—Allan, Rixford, Freeman and Brown reported this case as case 5 in their paper and Judd, Allan and Rynearson as case 7 in theirs. Multiple adenomas were found in the pancreas.

The patient, a man aged thirty two years, had had spells of weakness associated with mental confusion for a year. Hypoglycemia had been recognized elsewhere, and on advice sugar was eaten between meals and at night. Attacks were prevented by this means, but later the patient became unable to recognize prodromal symptoms and failed to resort to taking sugar until he was helpless. There also was a history of gastric distress

Examination at the clinic disclosed the presence of a duodenal ulcer When symptoms of hypoglycemia were present, the value for the blood sugar usually was less than 0 060 gm per 100 c c, however, on one occasion when a value of 0 040 was obtained the patient seemed normal.

Operation revealed two insular tumors which were removed One, measuring about 1 5 cm. in diameter, was embedded in the anterior surface of the pancreas, at the juncture of the tail and the body; the other, 2 0 cm in diameter, was 2 5 cm away from the first The pathologic examination yielded evidence of malignancy in these tissues, and because of the danger of metastasis a course of roentgen treatment was given. Recovery was without incident and complete relief was subsequently reported

Case 4.—This case, reported by Judd, Faust and Dixon, was the second case of insular tumor with extensive metastasis to come to our attention at the clinic.

The patient, a young woman eighteen years of age, was observed initially by Dr [illegible]
toms for thr [illegible]
sodes of dro [illegible]
that by eati [illegible]
weeks an attack resulted in loss of consciousness, and from then on repeated attacks occurred unless food was taken every two hours Thirty pounds (13 6 kg) had been added to the body weight because of frequent eating

The general examination at the clinic revealed evidence of a large liver, and on injection of bromsulfalein the retention of dye was grade 2 The value for the blood sugar in attacks of hypoglycemia was 0 045 gm per 100 c c. Results of a test of dextrose tolerance, made three hours after the patient had received 27 gm of sugar, were as follows: One gram of dextrose was administered per kilogram of body weight At the time this was given the value for blood sugar was 0 058 gm. per 100 c c, one half hour, one hour, one and one half hours and two and one-half hours afterward it was 0 125, 0 170, 0 160 and 0 127 respectively

The operation performed at The Mayo Clinic revealed a tumor in the pancreas and multiple metastatic growths in the liver One of the nodules was excised from the liver It was composed of entangled cords of large, clear cells with pale staining oval nuclei which contained multiple chromatic bodies or nucleoli and mitotic figures In the opinion of the pathologist the structure and arrangement of the tissue resembled that of embryonic islands of Langerhans

The patient recovered from the operation but died at home fifteen days later in a state of coma with convulsions Even large doses of dextrose given intravenously at frequent intervals had failed to prevent this terminal hypoglycemia. The request for a necropsy was refused

Case 5—This case was the third of insular tumor with multiple metastasis and the second in which proof of hyperinsulinism was provided by obtaining an extract with insulin-like activity from metastatic tissue It was reported by Power, Cragg and Lindem, by Cragg, Power and Lindem and by me.

[illegible]
h [illegible]
tc [illegible]
m [illegible]
fa [illegible]
sc [illegible]
busy preparing for a dinner party and omitted lunch In the evening, seating herself at table, she was overcome suddenly by extreme weakness and marked confusion Her muscles became rigid, especially those of the right

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A value for blood sugar obtained four hours after the patient had taken 200 c.c. of orange juice was 0 023 gm. per 100 c.c. The value for plasma sodium chloride was abnormally high (0 710 gm per 100 c.c); values for blood lipoids were low in the normal range. A test for dextrose tolerance resulted as follows. One gram of dextrose was administered per kilogram of body weight. The level of the blood sugar at the time dextrose was given was 0 035 gm per 100 c c; one half hour, two and three hours afterward, it was 0 088, 0 138 and 0 075 gm respectively.

Injection of 1 c c of 1.1,000 solution of epinephrine raised a blood sugar level of 0 043 gm per 100 c.c. to 0 110

At operation a well-encapsulated insular tumor was removed The liver was small, but not otherwise abnormal Although the gallbladder was full of stones it was not disturbed

The condition of the patient was satisfactory until the third postoperative day. Pneumonia then developed, and on the fifth day the patient died Permission for necropsy was refused The concentration of blood sugar postoperatively rose to diabetic levels Examination of the tumor showed it to be an adenocarcinoma of insular origin

Case 7.—This case was reported by Rynearson as case 2. Postponement of surgical treatment in this case as in case 6, led to marked changes in personality and to obesity, which contributed to a postoperative fatality from pneumonia

generalized epileptiform convulsions. In an early episode the patient was found unconscious in bed and continued to be unconscious for three days, until finally orange juice was fed forcibly In one attack boiling water was spilled on her bare arm, and although severely scalded the patient was not aroused When she came to the clinic she was taking daily 2 quarts (2,000 c c.) of orange juice, eating 2 teaspoonfuls of honey every half hour and sleeping with malted milk tablets in her mouth, all in addition to her regular meals The attacks were not prevented, however, and her weight

0 022 and consciousness was lost Abnormal hepatic function was revealed by a retention of dye grade 2 after injection of bromsulfalein

At operation an insular tumor 1.5 cm in diameter was removed without technical difficulty Mild hepatitis was noted The tumor was an adenocarcinoma grade 1 of insular origin After operation the blood sugar rose to diabetic levels and the patient died on the fourth postoperative day of pneumonia

Case 8.—In this case, since the patient had not noticed the relation of symptoms to fasting and their relief by food, spontaneous

arm and right leg. She perspired profusely and became rapidly more stuporous In fifteen minutes she was in a deep coma which lasted four hours She recovered spontaneously, but residual weakness of the right arm and leg persisted. The next day consciousness again was lost. This time she was comatose thirty hours, yet when Dr Cooley of Dubuque injected dextrose intravenously she recovered promptly, except for some slurring of speech and residual weakness of the right arm and leg.

On examination at the clinic January 30, 1935, the tendon reflexes of the legs were increased bilaterally and the fasting value for the blood sugar was 0.040 gm per 100 c c. A dextrose tolerance test, in which 1 gm of dextrose was administered per kilogram of body weight, resulted as follows: The concentration of blood sugar at the time dextrose was administered was 0 040 gm. per 100 c c; one-half hour afterward it was 0 132; two hours afterward it was 0 146 and three hours afterward, 0 059

Injection of 1 c c of 1:1,000 solution of epinephrine elevated a blood sugar level of 0 085 gm per 100 c c to 0.117, but 1 c c of a solution of pituitary extract (pituitrin) given intramuscularly was without effect

Hepatic function, as disclosed by galactose tolerance, hippuric acid and bromsulfalein tests was unimpaired, and the value for serum bilirubin was normal

At operation, February 6, 1935, the pancreas was found to be surrounded by dense masses of enlarged lymph nodes and the liver to contain multiple large metastatic growths, composed of cells resembling island cells.

The patient died five months later in Salt Lake City, where Dr. Lindem performed the necropsy The important tissues packed in carbon dioxide snow were sent to the clinic for examination. The insular origin of the carcinoma was established, and Dr Power confirmed the observation made in case 1 of insular activity in extracts of metastatic growth in the liver.

Case 6 —This case was reported by Rynearson as case 1 in his series of two cases.

minutes and recovered, but about three months later, when she was house cleaning, a similar episode occurred and she was unconscious for about twenty minutes Again she recovered spontaneously, but was extremely hungry and felt better after eating Attacks similar to these recurred every three or four months until 1933, and thereafter were more frequent. In August, 1933, a physician elsewhere had made a diagnosis of hyperinsulinism and together with other measures had prescribed frequent eating The patient did not improve, and for some months before she came to the clinic had averaged four attacks each twenty-four hours They lasted from one to five hours, and were followed by aphasia, dizziness and hunger Witnesses reported that in attacks the patient moaned loudly, had epileptiform convulsions and was very difficult to control. Aphasia, vertigo, hunger and desire to micturate were constantly present, and as a result of much eating the weight h. [illegible] In recent months [illegible] whipped her children

health remained good, however, and in contrast to other patients with chronic hypoglycemia who became obese, his weight remained practically stationary at about 170 pounds (77.1 kg).

"March 4, 1936, the patient returned to the Clinic. General examination was again negative. Dr. M. P. Foley, then associated with the Section on Neurology, suspected hypoglycemia and his suspicions were confirmed when the fasting value for blood sugar was determined to be 38 mg. per 100 c.c. The patient was hospitalized. In the course of his stay in the hospital determinations of blood sugar on subsequent occasions were as follows: 35, 44, 36, and 42 mg. per 100 c.c. As we have often noted in cases of this type, there was no necessary parallelism between the amount of sugar in the blood and the clinical condition. For example, on one occasion an attempt was made to induce an attack by withholding food. The patient received his last meal on the evening of March 10. The next morning the value for blood sugar was 44 mg., at 12 noon, it was 48 mg., and at 5 p.m. it was 35 mg. per 100 c.c. During most of this time he was up and about in the hospital, walking through the corridors, and appeared normal in spite of the fact that he had had no food whatsoever. At 2 p.m. he complained of hunger and, at 5 p.m., after a fast of twenty-three hours, his behavior suggested a mild hypoglycemic reaction. He then became somewhat irritable and confused, so that his fast was broken with orange juice, whereupon his symptoms disappeared. Except for the abnormal behavior of the blood sugar, examination was entirely negative. The bromsulphalein test of liver function gave normal results.

"Diagnosis of hypoglycemia of undetermined origin was made and exploratory operation was performed by one of us (Walters) on March 27. The pancreas was approached through an opening in the gastrocolic omentum just below the greater curvature of the stomach. The stomach was lifted upward and the pancreas was examined by palpation. An adenoma, approximately 2 cm. in diameter, was encountered at the juncture of the middle portion and tail of the pancreas directly over the inferior vena cava and abdominal aorta. The pancreas was elevated and the section containing the adenoma was removed. Pathologic examination of the excised portion of pancreas revealed an adenoma composed of practically normal pancreatic tissue. Examination of the abdominal contents disclosed nothing further. On the eleventh day after operation it was necessary to remove about 1,200 c.c. of fluid (apparently pancreatic in origin) which had accumulated posterior to the stomach in the lesser peritoneal cavity.

"The patient has since gradually made a complete recovery. A pancreatic fistula developed, but this practically has healed (May 15, 1936). At no time has the value for blood sugar been abnormal. Immediately after operation the value varied from 147 to 211 mg. per 100 c.c. Since that time it has varied from 115 to 168 mg. No sugar has appeared in the urine at any time."

A test of dextrose tolerance in this case, obtained before operation, gave the following results. The quantity of dextrose administered was 1 gm. per kilogram of body weight. At that time the level of the blood sugar was 0.036 gm. per 100 c.c. One half hour, two and three hours later it was 0.138, 0.079 and 0.054 respectively.

hypoglycemia was at first overlooked. The case is so instructive that I am quoting in full the fairly detailed account of it by Kepler and Walters:

"A farmer, aged forty-six years, had been in good health until the winter of 1933 and 1934, when he felt unusually tired and occasionally noticed blurring of vision March 20, 1934, he worked as usual until noon, returned to his home tired out, decided not to eat lunch and lay down on the davenport Sometime later he was found unconscious with both his arms and legs moving spasmodically. Recovery from this attack, about which the patient remembered nothing, was spontaneous and he remained well until August 4 On that morning he awoke feeling well but as he had overslept, he did not start the fire as usual but went outside carrying a cream pitcher and water bucket, as was his custom On arriving at the barn he found he was too late to assist with the milking, so he filled the pitcher with cream

he poured the cream into it and began washing his face in the cream The hired man then tried to carry him upstairs, but he refused assistance and almost fell getting up He undressed, went to bed, and awoke four hours later Of this entire incident he remembered practically nothing except the 'funny color of the wash water,' and his difficulty in getting upstairs

"August 22, 1934, the patient was brought to the Clinic for examination Nothing of significance was found, and a tentative diagnosis of an intracranial lesion was considered Encephalograms were made but they revealed nothing abnormal The patient was dismissed with instructions to *take ½ grain (0 032 gm) of phenobarbital at night and to return to the Clinic* for further study if the attacks recurred. By adhering to this regimen he remained fairly well during the next six months, and had had no more seizures but if he discontinued taking the phenobarbital he felt as if an attack were coming on In January, 1935, his wife wrote that he had just had another severe attack, that he complained a great deal about his vision and also that his hands were often numb

"Beginning in August, 1935, the patient's attacks occurred with increasing frequency and severity As a rule they came on about 4:30 a m , shortly after he had arisen and done the morning chores On some occasions he would lapse into an attack during sleep, at other times the attacks would occur just before lunch The outstanding feature of an attack was the patient's stubbornness and confusion He would yawn frequently and lapse into short naps Loss of consciousness with sweating and convulsions often followed The immediate ingestion of phenobarbital often would abort these symptoms Between episodes he often noticed that, when he was hungry, his vision would blur or his hands and feet would go to sleep February 23, 1936, he had a severe seizure, with convulsions and sweating, which lasted for twenty-four hours; after this he was given morphine and slept for an additional twenty-four hours *In addition to the symptoms* just mentioned he complained occasionally of short severe attacks of epigastric pain which were precipitated by turning his body to the right His general

Case 9.—This case has not previously been reported.

The patient, a man forty-three years of age, was from the Transvaal, South Africa When we saw him in 1936, he had had symptoms of episodic hypoglycemia for ten years, and two years before, in 1934, in London, England, hyperinsulinism had been diagnosed The only disturbance for a number of years had been an empty feeling between meals and before breakfast Finally an attack had occurred in church after a religious fast The patient was unconscious three hours and then recovered spontaneously Similar attacks followed with increasing frequency, and on the advice of physicians in London he increased the number of his meals to eight a day With the increased amount of food he had gained from 135 to 190 pounds (61.2 to 86 2 kg). A low carbohydrate diet had failed to help and had been abandoned.

The long duration of the history in this case prompted us to suspect hypoglycemia of other origin than hyperinsulinism. At operation, however, Dr. Walters found and removed a pancreatic adenoma 0.8 cm. in diameter. The patient died three days later with peritonitis and paralytic ileus, and necropsy revealed some fatty change in the liver. In the meantime, examination of the pancreatic adenoma indicated that it originated more probably from ductile than from insular epithelium. Opinion therefore remained divided as to the cause of the hypoglycemia. Abnormality of the adrenal glands or of the pituitary was not suggested by the appearance of these organs at necropsy, and except for the moderate fatty infiltration there was no good reason for incriminating the liver. Before the operation the hepatic function, so far as could be determined by the dye retention test and estimations of the serum bilirubin, had been normal. On the other hand, the histology of neoplastic pancreatic cells is admittedly ambiguous, and insular tumors not infrequently have been described as containing elements with ductile arrangement. Also, as so regularly has been seen in cases of insular tumor, the low value for blood sugar found preoperatively gave place immediately after removal of the tumor to values higher than normal (from 0.138 to 0.222 gm. per 100 c c.). To me the evidence as a whole establishes the diagnosis as hyperinsulinism.

Case 10—This case has not previously been reported. The duration of symptoms, nearly forty years, is unusual.

The patient, a man fifty five years of age, came to the clinic in 1937. From the age of sixteen he had had spells of weakness associated with hunger,

sweating, nervousness and thick speech They would be provoked by over working and for many years occurred infrequently None had led to loss of consciousness until about two years before the patient came to us By eating frequently he succeeded in avoiding many severe attacks, and thus had been able to continue his occupation as a purchasing agent

A fast test was tolerated remarkably well, no symptoms developed, even after twenty four hours, although at the end of this time the value for the blood sugar had fallen to 0 043 gm per 100 c c. The response to a dextrose tolerance test was as follows The quantity of dextrose administered was 1 gm. per kilogram of body weight The level of the blood sugar at the time dextrose was given was 0 079 gm per 100 c.c. One-half hour, one hour, two, three and four hours afterward it was 0 130, 0 216, 0 167, 0 105 and 0 067 respectively There were no symptoms on the day of this test, but on another day in a typical attack the value for the blood sugar was 0 051. The attack was characterized by disorientation, dysarthria, negativism and amnesia The patient resisted attempts to give him sugar, but when 20 c c. of a 50 per cent solution of dextrose was injected intravenously, except for complete loss of memory of the episode, he became normal almost at once.

At operation by Dr Walters an insular adenoma 1 cm in diameter was found and removed. Dr Walters also noted marked hepatitis and cirrhosis Despite this gross abnormality of the liver the patient remained entirely free from previous symptoms after operation, and the blood sugar level was not again abnormally depressed

Case 11.—This case is out of place chronologically It is included because the diagnosis, missed by us in 1930, was made elsewhere by Womack, Gnagi and Graham. An insular tumor was found and removed

The patient, a farmer aged forty four years, had had symptoms for ten months The complaint was of spells of mental confusion followed by amnesia They occurred usually before breakfast when he was milking He would wander into the house and lie down His wife would give him his breakfast or only a glass of milk He then would feel perfectly well, but could not remember what had happened A few days before he came to the clinic he collapsed, remained in a stupor for two or three hours, and recovered spontaneously

On examination in the clinic a brain tumor was suspected, but in the absence of localizing symptoms or evidence of intracranial pressure further observation was considered advisable, and the patient was dismissed with the injunction to return for another examination later. Soon afterward his wife discovered that by feeding him at night his early morning difficulty could be prevented. He also had taken to eating candy between meals before he was seen by the St. Louis physicians.

The operation in St Louis disclosed an insular tumor only 0 5 cm in diameter, yet the removal of this was followed by complete relief of the former symptoms The histologic appearance of the tumor was described by R. R. Bensley

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The patient, a man fifty-five years of age, came to the clinic in 1937 From the age of sixteen he had had spells of weakness associated with hunger,

sweating, nervousness and thick speech They would be provoked by overworking and for many years occurred infrequently. None had led to loss of consciousness until about two years before the patient came to us By eating frequently he succeeded in avoiding many severe attacks, and thus had been able to continue his occupation as a purchasing agent

A fast test was tolerated remarkably well, no symptoms developed, even after twenty four hours, although at the end of this time the value for the blood sugar had fallen to 0 043 gm per 100 c.c. The response to a dextrose tolerance test was as follows The quantity of dextrose administered was 1 gm. per kilogram of body weight The level of the blood sugar at the time dextrose was given was 0 079 gm per 100 c c One half hour, one hour, two, three and four hours afterward it was 0 130, 0 216, 0 167, 0 105 and 0 067 respectively. There were no symptoms on the day of this test, but on another day in a typical attack the value for the blood sugar was 0 051. The attack was characterized by disorientation, dysarthria, negativism and amnesia The patient resisted attempts to give him sugar, but when 20 c.c. of a 50 per cent solution of dextrose was injected intravenously, except for complete loss of memory of the episode, he became normal almost at once

At operation by Dr Walters an insular adenoma 1 cm in diameter was found and removed. Dr Walters also noted marked hepatitis and cirrhosis. Despite this gross abnormality of the liver the patient remained entirely free from previous symptoms after operation, and the blood sugar level was not again abnormally depressed.

Case 11.—This case is out of place chronologically It is included because the diagnosis, missed by us in 1930, was made elsewhere by Womack, Gnagi and Graham. An insular tumor was found and removed.

The patient, a farmer aged forty-four years, had had symptoms for ten months The complaint was of spells of mental confusion followed by amnesia They occurred usually before breakfast when he was milking He would wander into the house and lie down His wife would give him his breakfast or only a glass of milk He then would feel perfectly well, but could not remember what had happened. A few days before he came to the clinic he collapsed, remained in a stupor for two or three hours, and recovered spontaneously.

On examination in the clinic a brain tumor was suspected, but in the absence of localizing symptoms or evidence of intracranial pressure further observation was considered advisable, and the patient was dismissed with the injunction to return for another examination later Soon afterward his wife discovered that by feeding him at night his early morning difficulty could be prevented He also had taken to eating candy between meals before he was seen by the St Louis physicians.

The operation in St Louis disclosed an insular tumor only 0 5 cm. in diameter, yet the removal of this was followed by complete relief of the former symptoms The histologic appearance of the tumor was described by R. R. Bensley.

Case 12.—This case which has not previously been reported is unusual because of the age of the patient.

The patient, a Jewish boy nine and a half years of age, had previously been free from abnormalities. He was found in bed by his mother one morning unresponsive, but with wide-open eyes. Obeying an unexplained inspiration, the mother forcibly fed the boy some orange juice and cereal, and in fifteen minutes he had recovered completely. This was in January, 1938. A second similar episode occurred six weeks later, again in the early morning; involuntary urination was associated The child was again revived with orange juice and cereal, and went to school feeling well A third attack occurred in May. Like the previous ones it developed at an early morning hour.

The boy was sent to a Scout Camp in June, 1938, and there one morning about 11 o'clock, after a period of unusual vigorous exertion, he was found unconscious No food being given, he remained unconscious for seven hours, then recovered spontaneously This severe reaction led to a consultation with an experienced physician who correctly diagnosed hyperinsulinism and prescribed frequent feedings Attacks continued, and as time passed they became increasingly difficult to prevent. Also some time later they [illegible]

[illegible] 9 A preliminary exam[illegible] unusual other than a sugg[illegible] before breakfast Values for sodium and potassium in the blood serum were 0.305 and 0.019 gm per 100 c c respectively The response to an extended dextrose tolerance test was as follows. The quantity of dextrose given was 1 gm. per kilogram of body weight At the time the dextrose was given the level of the blood sugar was 0.046 gm. per 100 c c. At the end of one-half hour it was 0.100, at one hour, 0.115, at one and one-half hour, 0.125; at two hours, 0.118, at two and one-half hours, 0.084, at three and one-half hours, 0.050; at four and one-half hours, 0.045, and at five and one-half hours, 0.042. At the four and a half hour period, the patient developed symptoms, at the fifth hour period these became so severe that emergency treatment with sugar could no longer be withheld.

At operation by Dr Walters a small tumor was found in the pancreas, and microscopic examination of this after its removal revealed it to be a small insular adenoma The postoperative course was uneventful except for temporary hyperglycemia and glycosuria One hour after the operation the level of blood sugar was 0.221 gm. per 100 c c and four or five hours later it was 0.256 For the whole of this day and during the night the urine gave strong reactions for sugar, but negative reactions for acetone and diacetic acid. Insulin purposely was not administered; by the next morning the urine was sugar free, and within forty-eight hours all blood sugar values were normal. The subsequent recovery of the patient was apparently complete. Normal feeding could be resumed without extra feeding at night and no further evidence of a tendency to hypoglycemia could be obtained The operation apparently could be regarded as curative.

SUMMARY OF EXPERIENCE

To review these twelve cases is instructive, but somewhat discouraging. My colleagues and I are not proud of the record, although probably it is no worse than should be expected. It illustrates the difficulty of diagnosis in this disease, the danger of postponing operation when insular tumor exists, and the relatively serious surgical risk when hypoglycemic attacks with convulsions have led to gross obesity or to damage of the brain.

Of the twelve patients only six have survived These apparently were cured. In two cases we missed the diagnosis. In one of them we recognized the disease at a later examination, in the other the correct diagnosis was made elsewhere In both instances the mistake can be attributed to failure on the part of examining physicians simply to hold in mind the possibility of spontaneous hypoglycemia This possibility must always be considered when symptoms suggestive of brain tumor or other disease of the nervous system are present.

In several of the cases with isolated and seemingly benign tumors microscopic examination revealed minor evidence of malignancy, while in three cases metastasis already had occurred at the time of the surgical exploration, and inoperable conditions were found.

In three cases resection of tumors resulted fatally. The cause of death in two was pneumonia, in the third peritonitis In two of these three fatal cases the gross obesity that had resulted from years of attempting to control symptoms by frequent feeding contributed to the difficulty of the operation and to the risk of postoperative complications. In two of the fatal cases permanent change of personality suggested that the damage done to the brain may have lowered resistance to operative complication.

A serious impediment to successful recognition and early treatment of insular neoplasm is the frequency with which nothing abnormal is found in the pancreas at operation, in cases indistinguishable clinically from those in which insular tumors are found. In the period from 1927 to September 1, 1939 a normal appearing pancreas was disclosed by exploratory operation in fifteen such cases. Marked cirrhosis existed in two of them and cholecystitis with stones in a third. A finding of hepatitis with infiltration of fat in two cases, reported by Judd, Kepler and

Rynearson, led us to believe that in them we might be dealing with some peculiarly isolated disturbance of the glycogenic function of the liver. However, this remains conjectural for the reason that in several of the cases in which an insular tumor was found hepatitis also was present, and the removal of the tumor corrected the hypoglycemia. Finally, some degree of resection of a normal looking pancreas has been performed in several cases, with a beneficial result in at least two of them. On the other hand, in another case reported by Judd, Allan and Rynearson[4] in 1933, three attempts were made to remove pancreatic tissue, and even after the third operation the patient had not been helped.[5]

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[4] This case later was given further consideration by Carlson and Rynearson.

[5] [illegible] in The Mayo Clinic in the period 1927 to [illegible] nosis of [illegible] reason [illegible] nosis of hyperinsulinism was made in the twelve-year period considered, total thirty seven, divided as follows: hyperinsulinism was established by finding an insular tumor in twelve cases, hyperinsulinism was suspected but at operation the pancreas appeared normal and hepatic lesions were found in five, hyperinsulinism was sus- [illegible]

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CHAPTER XXVI

TREATMENT OF HYPERINSULINISM

The *medical treatment of hyperinsulinism can be only* symptomatic and directed at correction of hypoglycemia. It is essentially the same as that required for any form of hypoglycemia *but unfortunately is frequently ineffective.* Hence, if the presence of true hyperinsulinism is seriously suspected surgical intervention should be undertaken.

DIETARY MANAGEMENT OF HYPOGLYCEMIA

The immediate remedy for an excessively low level of the blood sugar is administration either of dextrose or of a sugar or polysaccharide that readily is converted into dextrose[1] The patient with spontaneous hypoglycemia may learn this himself, if he is prompted by the hunger that so often is experienced when the level of the blood sugar falls severely. He finds that eating relieves not only his hunger but other symptoms, and thereafter continues to take milk, fruit juice or a carbohydrate containing food whenever he notices these symptoms. By this means, even in some cases of insular tumor, serious attacks may be warded off for years.

Carbohydrate foods promptly raise the level of the blood sugar. Ingestion of sugar in cases of hypoglycemia of nervous origin, however, provokes more trouble an hour or two later. The hypoglycemic phase of the blood sugar time curves of dextrose tolerance tests, was mentioned in Chapter XXIII. Furthermore, in many mild cases of spontaneous hypoglycemia of nervous origin diets rich in carbohydrate seem to increase the instability of the already uneven regulation of blood sugar, and thus promote more frequent attacks of hypoglycemia. When sugar is given to combat the symptoms of an attack in these cases, only enough should be used to obtain results. Also whenever possible the diet should be made relatively low in carbohydrate and high in fat and protein

[1] This subject is given more extensive consideration in Chapter VI

The advantage of a high fat diet in the management of spontaneous hypoglycemia was first called to my attention by a former dietetic assistant, Miss Florence Smith. By adopting her suggestion we were able successfully to treat the relatively mild hypoglycemia of nervous origin Later Waters and Shepardson advised such a diet Waters, and also Weil, prescribed six meals a day. On this regimen there often was great improvement, but the attacks, although diminished in number, were rarely prevented With hypoglycemia of greater severity, such as is encountered in cases of insular tumor, these procedures usually fail completely

The advantage of a diet high in protein was pointed out by Conn. With Newburgh, Conn demonstrated that despite the conversion of approximately 50 per cent of its weight to dextrose, ingestion of protein in large amounts causes relatively little, if any, rise in the level of the blood sugar of both normal and diabetic persons A quantity of dextrose or starch equivalent to that obtainable by conversion in the body from the amount of protein used would cause marked hyperglycemia The difference was accounted for by the slow speed with which dextrose is made from protein, and the advantage of feedings of protein was attributed to this release of dextrose at so slow a rate that it did not "stimulate the pancreas to produce more insulin." The comparative effect of ingestion of dextrose and of protein on the blood sugar in a case of spontaneous hypoglycemia is shown in figure 19 After a dose of 1 gm. of dextrose per kilogram of body weight a hypoglycemic phase follows a brief period of hyperglycemia, whereas after sufficient protein to yield the same amount of dextrose the level of the blood sugar remains essentially unchanged for a period of eight hours. The gradual and prolonged rise of the blood urea nitrogen reflects the utilization of protein and the slow liberation of dextrose into the blood.

Another therapeutic suggestion based on the same principle of dampening the activity of the pancreas was made by John This was to give insulin by injection one-half hour after each of three equally divided low carbohydrate meals.

The best results at The Mayo Clinic have been obtained with a diet planned like the standard diabetic diets described in Chapter VII, but with more protein (about 2 gm. per kilogram of body weight) and more frequent meals The diet is divided into three

large meals of equal composition, and three smaller meals each with half the amount of carbohydrate, protein and fat contained in the larger meals. We have not used insulin, and prefer milk

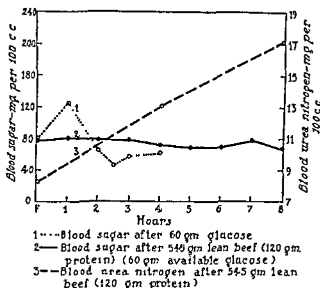


Fig 19—Comparison of effect on the level of the blood sugar of ingestion of 60 gm of glucose and of sufficient protein to yield 60 gm. of dextrose in the body [Redrawn from Conn, J W.: J Clin. Investigation, *15:* 673–678 (Nov) 1936]

and bread to fruit juice or raw sugar for the emergency treatment of any attacks that the diet fails to prevent.[2]

MEDICATION

In severe cases of spontaneous hypoglycemia, when the diet alone is ineffective, drugs may be used. On the basis of theory the one that should offer the greatest advantage is the diabetogenic hormone of the anterior lobe of the pituitary body, but unfortunately a preparation of diabetogenic pituitary hormone suitable for clinical use is not commercially available. Cortical hormone also ought to help through its diabetogenic activity, but

heretofore its cost has been prohibitive. The recently synthesized preparation desoxycorticosterone acetate does not seem to possess any diabetogenic activity. Desiccated thyroid and thyroxin have been tried, and if enough of either of them is given to maintain a metabolic rate of +20 or +30 per cent, attacks may be prevented. A serious objection is the harm that may result from the continuous maintenance of such a stimulated metabolism. Epinephrine is useful in the treatment of an attack if followed immediately by a dose of dextrose, but its action is far too transitory to be beneficial otherwise. The use of epinephrine in oil has been suggested, but experience with it in cases of this kind is lacking. Although pituitrin has some antagonistic effect on the action of insulin, preparations of posterior lobe of the pituitary have not been of value in warding off attacks. Harris (1933) reported that ephedrine gave doubtful results. We have not had success with it. Harris suggested that bromides may depress the secretion of insulin, but because of the danger of brominism he did not advise their use Harris also thought that phenobarbital might depress the activity of the islands of Langerhans, and suggested doses of 1½ grain (0.1 gm.) night and morning Phenobarbital apparently was somewhat effective in one of our cases. Belladonna or atropine in sufficiently large doses will decrease the secretion of ptyalin and gastric juice, and may similarly affect the internal secretion of the pancreas. Harris used it in mild cases of spontaneous hypoglycemia with what he regarded as good results. Caffeine, as Womack has suggested, may be of some value in stimulating the adrenal glands

EXERCISE

An important consideration for the patient who has attacks of spontaneous hypoglycemia, of whatever origin, is the matter of exercise. Physical exertion lowers the level of the blood sugar and therefore must be curtailed, or at least the patient must be warned to be on his guard whenever he does exercise and to protect himself by eating something, preferably a starchy food, before exerting himself.

SURGICAL TREATMENT

The dietary and the other measures described are fully effective only in cases with mild attacks of hypoglycemia. In severe

cases they are unavailing. The patient because of frequent eating to prevent attacks often becomes obese and thereby the hazard of operation is increased. For these reasons, as well as because delay may result in the metastatic extension of malignant insular tumors which are removable if operation is performed early, it is wise in severe cases when the cause of the hypoglycemia is not clearly extra-insular to advocate early surgical exploration.[3]

For patients who have not become grossly overweight operation for the removal of insular adenoma is not attended with unusual risk. The surgical procedure has been described by Judd, Allan and Rynearson, Graham and Womack, Simon, Whipple and Frantz, and others. It must not be forgotten that multiple tumors occasionally exist. Graham in one case resected a small insular tumor; the symptoms persisted. At a second operation a second tumor was found and its removal was followed by complete recovery.

When he can find no tumor, the surgeon is faced with the question as to whether he should try to diminish the activity of the pancreas as a whole. Failure to find a tumor does not mean that one is not present.[4] The consistency of an insular adenoma differs very little from that of the pancreas, and a small adenoma buried in the head or body of the pancreas may easily escape detection. For this reason, as well as because the removal of a large enough portion of the pancreas possibly may be of benefit in cases of hyperfunction of normal appearing islands, a subtotal resection of the pancreas may be attempted. The earlier operations of this kind were unsuccessful, but striking benefit from such procedures have been reported by Thomason, by Berry, by Graham and Hartmann, and by others.

In a Colver lecture delivered in 1932 (Wilder, 1933) I pointed out that a situation existed in this disease analogous to that in surgery for hyperthyroidism, and that the early surgical failures in both diseases were attributable to resection of an inadequate

[3] Care must be taken to exclude adrenal insufficiency (Addison's disease). Patients with Addison's disease stand surgical procedures poorly unless special precautions are observed (Wilder, 1938). The same applies to patients with insufficiency of the anterior lobe of the pituitary.

[4] Whipple reoperated in four cases in which an earlier exploration had revealed no tumor and resection had not brought relief. In each case he found an adenoma in the posterior aspect of the head of the pancreas after mobilizing the duodenum.

amount of tissue. In the case reported by Graham and Hartmann a girl baby twelve months old had convulsions and the very low value for sugar in the capillary blood of 0.18 gm. per 100 c.c. The pancreas was normal in appearance, and as much of it was resected as possible, leaving a remnant in the curve of the duodenum which was estimated to be less than one-eighth of the whole. A careful survey of the tissue gave no evidence of neoplastic growth, and so far as could be judged the islands of Langerhans were normal in size and number. Nevertheless, after the operation the blood sugar rose to abnormally high values. It later returned to normal, but not to hypoglycemic values, and the child two years later appeared to be perfectly healthy.

Thomason, finding no tumor in a case of severe spontaneous hypoglycemia, removed all but a part of the head of the pancreas He accomplished this by following a suggestion of Holman and Railsback, namely by first ligating the splenic artery so as to prevent hemorrhage from its branches to the pancreas and then removing the spleen and dissecting the tail and body of the gland. The body of the pancreas was severed from the head with Percy cautery. A year later the patient was free from his previous symptoms; the fasting value of his blood sugar was 0 087 gm per 100 c.c.

Another possible mode of attack, when no tumor can be found, is to place a strong ligature around the pancreas, as close as possible to the head. This effects necrotic degeneration of that part of the organ distal to the ligature. It was done by Dr Walters in a case in our series in which no tumor could be found, and thereby severe spontaneous hypoglycemia was converted into a mild diabetes. Exception may be taken in principle to attempts to cure one disease by creating another, but in this instance I believe it to be excusable Diabetes can be treated effectively, spontaneous hypoglycemia when severe is much more debilitating than diabetes and less amenable to management.

The course after these operations on the pancreas usually has not been troublesome The use of ether as the anesthetic agent is desirable for the same reason that ether is undesirable in operations on patients who have diabetes, namely that it tends to elevate the level of the blood sugar. After operations in which ether has been given, there has been little or no difficulty in maintaining

the blood sugar at a safe level for the twenty-four to seventy-two hours before the patient can be given food. On the other hand, two patients at The Mayo Clinic developed pneumonia after removal of an insular tumor, for which the anesthetic agent (ether) might have been in part to blame. Hyperglycemia and glycosuria may develop after the removal of an insular tumor. They are not severe and persist only for two or three days. The occurrence after operation of a pancreatic fistula has delayed recovery in a few cases, but healing eventually has occurred and with careful suturing of the pancreas a fistula usually is avoidable.

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APPENDIX*

APPROXIMATE EQUIVALENTS

1 gram (gm)	= 1/30 ounce
1 kilogram (kg) (1,000 gm)	= 2 2 pounds
1 cubic centimeter (c c)	= 1/30 fluidounce
1 liter (L.) (1,000 c c)	= 1 quart plus 1⅔ fluidounces
1 degree centigrade (1° C)	= 1 8 degrees Fahrenheit
1 calorie (cal)	= 4 British thermal units (B T U)

To convert ounces to grams, multiply the ounces by 30.

To convert pounds to kilograms, divide the pounds by 2 2, or consult Scale I, Food Nomogram.

Household measures.

1 teaspoonful of fluid = 5 c c

TABLES OF FOOD VALUES

The composition of the foods in most common use is to be found in the following tables. More complete food lists are contained in Bulletin 28, Circular 146 and Circular 50, United States Department of Agriculture. These pamphlets can be obtained from the Superintendent of Documents, Government Printing Office, Washington, D. C, for ten cents each in coin

In Table 10 a variety of vegetables and fruits are classified according to their percentage content of carbohydrate.

Fruits canned without sugar have one-half the carbohydrate content of fresh fruits if an equal amount of fruit and water are used in canning. Fruits packed in their own juice have the same carbohydrate value as the fresh fruits.

In the process of cooking, foods lose both in weight and in content of carbohydrate, due to loss of water and dissolving out of carbohydrate These losses approximately balance each other, and so foods may be weighed either before or after cooking, pro-

* Reprinted except for Table 16 from Wilder R M · A primer for diabetic patients Ed 6, Philadelphia, W. B. Saunders Co., 1937.

TABLE 10

VEGETABLES

3 per cent	6 per cent	15 per cent	20 per cent
Asparagus	Beets	Artichokes	Corn
Beet greens	Carrots	Green peas	Hominy, cooked
Broccoli	Kohlrabi	Parsnips	Lima beans, canned
Brussels sprouts	Onions		Macaroni, cooked
Cabbage	Pumpkin		Noodles, cooked
Cauliflower	Rutabagas		Potato
Celery	Hubbard or winter squash		Rice, boiled
Cucumbers	Turnips		Shelled beans, cooked
Dandelion greens			Spaghetti, cooked
Eggplant			
Endive			
Green peppers			
Lettuce			
Mushrooms			
Radishes			
Sauerkraut			
Spinach			
String beans			
Summer squash			
Swiss chard			
Tomato			
Water cress			

FRUITS

5 per cent	10 per cent	15 per cent	20 per cent
Apricots*	Blackberries	Apples	Bananas
Blackberries*	Cantaloupe	Apricots	Grapes
Cherries, red or white*	Cherries, black*	Blueberries	Plums
Loganberries*	Cranberries	Cherries	
Peaches*	Grapefruit	Currants	
Raspberries*	Gooseberries	Huckleberries	
Rhubarb, fresh	Grapes, white*	Pears	
Strawberries*	Lemons	Raspberries	
	Oranges		
	Pears*		
	Peaches		
	Pineapple		
	Pineapple*		
	Strawberries		
	Watermelon		

* Canned without sugar

vided the water in which they are cooked is discarded When they are served in the water in which they are cooked, as in the case with stewed rhubarb, vegetable soups and stewed fruits, they should be weighed before cooking.

In Table 11 percentage composition (grams in each 100 gm.) of carbohydrate, protein and fat is given for a wide variety of

foods. The figures for carbohydrate represent only available carbohydrate.

TABLE 11

COMPOSITION OF VARIOUS FOODS

	Average composition of 100 gm		
Vegetables and fruits	Carbohydrate gm	Protein, gm	Fat, gm
3 per cent vegetables	3	1	0
6 per cent vegetables	6	1	0
15 per cent vegetables	15	2	0
20 per cent vegetables			
Potato	20	2	0
Shelled beans	20	7	0
Green corn	20	3	1
5 per cent fruits	5	1	0
10 per cent fruits	10	1	0
15 per cent fruits	15	1	0
20 per cent fruits	20	2	0
Green olives	2	1	10
Ripe olives	4	1	20
Cereals and breadstuffs			
Breakfast cereals, dry	80	10	5
Breakfast cereals, cooked	11	1	0
White bread	53	9	2
Whole wheat bread	49	10	1
Rye bread	53	9	1
Wheat flour	76	8	1
Soda crackers	73	10	9
Soy beans	8	38	15
Dairy products			
Whole milk	5	3	4
Skimmed milk	5	3	1
Cream, 20 per cent fat	5	3	20
Cream, 30 per cent fat	4	3	30
Cream, 40 per cent fat	3	2	40
Buttermilk	5	3	1
Cheese	0	29	36
Cottage cheese	4	21	1
Eggs, each	0	6	6
Egg white (one)	0	3	0
Egg yolk (one)	0	3	6

TABLE 11 (continued)

	Average composition of 100 gm.		
Meats and fish	Carbohydrate, gm.	Protein, gm	Fat, gm.
Meat, cooked	0	25	15
Fat meat, cooked	0	25	30
Fish (halibut, lake trout, perch, white fish)	0	18	5
Fish (salmon, fresh or canned)	0	22	13
Oysters	4	6	1
Liver	2	20	3
Fat bacon	0	10	67
Lean bacon	0	16	43
Cooked bacon	0	25	50
Fats:			
Butter	0	0	85
Lard, *tallow*, *oleomargarine*, *crisco*, bacon fat	0	0	85–100
Olive oil and other oils	0	0	100
Mayonnaise (see recipe, p 133)	0	0	85
Peanut butter	6	29	46
Nuts:			
Butternuts	3	28	61
Brazil nuts	7	17	67
Hickory nuts	11	15	67
Black walnuts	12	28	56
Pecans	13	11	71
Filberts	13	16	65
Beechnuts	13	22	57
English walnuts	16	17	63
Almonds	3	21	55
Peanuts	6	30	50
Chestnuts	42	6	5

HEIGHT-WEIGHT-AGE TABLES

TABLE 12

AVERAGE HEIGHT—WEIGHT—AGE TABLE (MEN)

GRADED AVERAGE WEIGHT

Age.	5 ft.	5 ft. 1 in.	5 ft. 2 in.	5 ft. 3 in.	5 ft. 4 in.	5 ft. 5 in.	5 ft. 6 in.	5 ft. 7 in.	5 ft. 8 in.	5 ft. 9 in.	5 ft. 10 in.	5 ft. 11 in.	6 ft.	6 ft. 1 in.	6 ft. 2 in.	6 ft. 3 in.	6 ft. 4 in.	6 ft. 5 in.
5																		
6																		
17																		
18																		
19																		
20																		
21																		
22																		
23																		
24																		
25																		
26																		
27																		
28																		
29																		
30																		
31																		
32																		
33																		
34																		
35																		
36																		
37																		
38																		
39																		
40																		
41																		
42																		
43																		
44																		
45																		
46																		
47																		
48																		
49																		
50																		
51																		
52																		
53																		
54																		
55 and up	135	137	139	142	145	149	153	158	163	168	173	178	184	191	198	205	212	219

Reprinted from Medico-Actuarial Mortality Investigation, Vol I, New York, 1912

When taking measurements remove the outdoor clothing, shoes and coat.

Age is taken to the nearest birthday.

TABLE 13

AVERAGE HEIGHT—WEIGHT—AGE TABLE (WOMEN)

GRADED AVERAGE WEIGHT

Age.	4 ft. 8 in.	4 ft. 9 in.	4 ft. 10 in.	4 ft. 11 in.	5 ft.	5 ft. 1 in.	5 ft. 2 in.	5 ft. 3 in.	5 ft. 4 in.	5 ft. 5 in.	5 ft. 6 in.	5 ft. 7 in.	5 ft. 8 in.	5 ft. 9 in.	5 ft. 10 in.	5 ft. 11 in.	6 ft.
15	101	103	105														
16	102	104	106														
17	103	105	107														
18	104	106	109														
19	105	107	109														
20																	
21																	
22																	
23																	
24																	
25																	
26																	
27																	
28																	
29																	
30																	
31																	
32																	
33																	
34																	
35																	
36																	
37																	
38																	
39																	
40																	
41																	
42																	
43																	
44																	
45																	
46																	
47																	
48																	
49																	
50																	
51																	
52																	
53																	
54																	
55																	

Reprinted from Medico-Actuarial Mortality Investigation, Vol I, New York, 1912

When taking measurements remove the outdoor clothing and shoes.

Age is taken to the nearest birthday.

TABLE 14

Height—Weight—Age Table (Boys)

Height inches	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs	11 yrs	12 yrs	13 yrs	14 yrs	15 yrs	16 yrs	17 yrs	18 yrs	19 yrs
38	34	34													
39	35	35													
40	36	36													
41	38	38	38												
42	39	39	39	39											
43	41	41	41	41											
44	44	44	44	44											
45	46	46	46	46	46										
46	47	48	48	48	48										
47	49	50	50	50	50	50									
48		52	53	53	53	53									
49		55	55	55	55	55	55								
50		57	58	58	58	58	58	58							
51			61	61	61	61	61	61							
52			63	64	64	64	64	64	64						
53			66	67	67	67	67	68	68						
54				70	70	70	70	71	71	72					
55				72	72	73	73	74	74	74					
56				75	76	77	77	77	78	78	80				
57					79	80	81	81	82	83	83				
58					83	84	84	85	85	86	87				
59						87	88	89	89	90	90	90			
60						91	92	92	93	94	95	96			
61							95	96	97	99	100	103	106		
62							100	101	102	103	104	107	111	116	
63							105	106	107	108	110	113	118	123	127
64								109	111	113	115	117	121	126	130
65								114	117	118	120	122	127	131	134
66									119	122	125	128	132	136	139
67									124	128	130	134	136	139	142
68										134	134	137	141	143	147
69										137	139	143	146	149	152
70										143	144	145	148	151	155
71										148	150	151	152	154	159
72											153	155	156	158	163
73											157	160	162	164	167
74											160	164	165	170	171

Prepared by Bird T Baldwin, Ph D, and Thomas D Wood, M D

TABLE 15

HEIGHT—WEIGHT—AGE TABLE (GIRLS)

Height inches	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs.	10 yrs	11 yrs	12 yrs	13 yrs	14 yrs.	15 yrs.	16 yrs	17 yrs	
38	33	33												
39	34	34												
40	36	36	36											
41	37	37	37											
42	39	39	39											
43	41	41	41	41										
44	42	42	42	42										
45	45	45	45	45	45									
46	47	47	47	48	48									
47	49	50	50	50	50	50								
48		52	52	52	52	53	53							
49		54	54	55	55	56	56							
50		56	56	57	58	59	61	62						
51			59	60	61	61	63	65						
52			63	64	64	64	65	67						
53			66	67	67	68	68	69	71					
54				69	70	70	71	71	73					
55				72	74	74	74	75	77	78				
56					76	78	78	79	81	83				
57					80	82	82	82	84	88	92			
58						84	86	86	88	93	96	101		
59						87	90	90	92	96	100	103	104	
60						91	95	95	97	101	105	108	109	111
61							99	100	101	105	108	112	113	116
62							104	105	106	109	113	115	117	118
63								110	110	112	116	117	119	120
64								114	115	117	119	120	122	123
65								118	120	121	122	123	125	126
66									124	124	125	128	129	130
67									128	130	131	133	133	135
68									131	133	135	136	138	138
69										135	137	138	140	142
70										136	138	140	142	144
71										138	140	142	144	145

Prepared by Bird T Baldwin, Ph D , and Thomas D. Wood, M D.

TABLE 16

HEIGHT—WEIGHT—AGE TABLE

(CHILDREN BETWEEN ONE AND FOUR YEARS—WITHOUT CLOTHES)*

5,602 boys.		Age months	4 821 girls	
Height, inches.	Weight, pounds.		Height inches	Weight, pounds.
26 5	18 0	6	25 9	16 8
27 3	19 1	7	26 5	17 4
27 6	19 8	8	27 0	18 3
28 1	20 4	9	27 6	19 1
28 5	20 9	10	27 9	19 5
29 0	21 4	11	28 4	20 1
29 4	21 9	12	28 9	20 8
29 9	22 9	13	29 4	21 0
30 3	23 0	14	29 5	21 6
30 8	23 6	15	30 1	21 9
31 1	24 1	16	30 5	22 6
31 4	24 5	17	30 8	22 9
31 8	24 8	18	31 1	23 4
32 3	25 5	19	31 5	23 8
32 6	25 8	20	32 0	24 1
32 9	25 8	21	32 5	24 6
33 3	26 9	22	32 6	25 3
33 6	27 0	23	32 9	25 6
33 8	27 1	24	33 4	26 4
34 0	27 9	25	33 8	26 9
34 1	28 3	26	33 9	27 3
34 8	29 0	27	33 9	27 3
35 1	29 1	28	34 6	27 8
35 4	29 3	29	34 8	27 8
35 4	29 5	30	34 9	28 3
35 6	30 3	31	35 1	28 8
36 0	30 6	32	35 4	29 0
36 1	30 6	33	35 6	29 1
36 5	31 1	34	36 5	30 1
36 8	31 9	35	36 5	30 3
37 1	32 3	36	36 8	30 5
37 4	32 3	37	36 8	30 8
37 5	32 4	38	37 0	31 0
37 9	33 1	39	37 3	31 6
38 5	33 5	40	37 5	32 0

* Reprinted from Crum, F S Quarterly Publication of the American Statistical Association, Boston, September, 1916, N S No 115, 15, 358.

TABLE 15

Height—Weight—Age Table (Girls)

Height inches	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs	11 yrs	12 yrs	13 yrs.	14 yrs.	15 yrs	16 yrs	17 yrs	18 yrs
38	33	33												
39	34	34												
40	36	36	36											
41	37	37	37											
42	39	39	39											
43	41	41	41	41										
44	42	42	42	42										
45	45	45	45	45	45									
46	47	47	47	48	48									
47	49	50	50	50	50	50								
48		52	52	52	52	53	53							
49		54	54	55	55	56	56							
50		56	56	57	58	59	61	62						
51			59	60	61	61	63	65						
52			63	64	64	64	65	67						
53			66	67	67	68	68	69	71					
54				69	70	70	71	71	73					
55				72	74	74	74	75	77	78				
56					76	78	78	79	81	83				
57					80	82	82	82	84	87	92			
58						84	86	86	88	93	96	101		
59						87	90	90	92	96	100	103	104	
60						91	95	95	97	101	105	108	109	111
61														
62														
63														
64														
65								118	120	121	122	123	125	126
66									124	124	125	128	129	130
67									128	130	131	133	133	135
68									131	133	135	136	135	138
69										135	137	138	140	142
70										136	138	140	142	144
71										138	140	142	144	145

Prepared by Bird T Baldwin, Ph D, and Thomas D. Wood, M. D.

TABLE 16

Height—Weight—Age Table

(Children Between One and Four Years—Without Clothes)*

5,602 boys		Age, months.	4,821 girls.	
Height, inches	Weight, pounds		Height, inches.	Weight, pounds.
26 5	18 0	6	25 9	16 8
27 3	19 1	7	26 5	17 4
27 6	19 8	8	27 0	18 3
28 1	20 4	9	27 6	19 1
28 5	20 9	10	27 9	19 5
29 0	21 4	11	28 4	20 1
29 4	21 9	12	28 9	20 8
29 9	22 9	13	29 4	21 0
30 3	23 0	14	29 5	21 6
30 8	23 6	15	30 1	21 9
31 1	24 1	16	30 5	22 6
31 4	24 5	17	30 8	22 9
31 8	24 6	18	31 1	23 4
32 3	25 5	19	31 5	23 8
32 6	25 8	20	32 0	24 1
32 9	25 8	21	32 3	24 8
33 3	26 9	22	32 6	25 3
33 6	27 0	23	32 9	25 6
33 8	27 1	24	33 4	26 4
34 0	27 9	25	33 6	26 9
34 1	28 3	26	33 9	27 3
34 8	29 0	27	33 9	27 3
35 1	29 1	98	34 6	27 6
35 4	29 3	29	34 8	27 8
35 4	29 5	30	34 9	28 3
35 5	30 5	31	35 1	28 8
36 0	30 6	32	35 4	29 0
36 1	30 6	33	35 6	29 1
36 5	31 1	34	36 3	30 1
96 8	31 9	35	36 5	30 3
37 1	32 3	36	36 8	30 5
37 4	32 3	37	36 8	30 8
37 5	32 4	38	37 0	31 0
37 9	33 1	39	37 3	31 6
38 5	33 5	40	37 5	32 0

* Reprinted from Crum, F S Quarterly Publication of the American Statistical Association Boston, September, 1916, N S, No 115 15 352

TABLE 16 (*Continued*)

5,602 boys.		Age, months	4,821 girls.	
Height, inches	Weight, pounds		Height, inches	Weight, pounds.
38 6	33 6	41	37 8	32 3
38 6	33 8	42	38 0	32 5
38 8	33 8	43	38 3	32 8
38 9	34 3	44	38 5	33 0
39 0	34 5	45	38 5	33 5
39 0	34 8	46	38 8	33 5
39 3	35 8	47	38 9	33 5
39 5	35 9	48	39 0	33 8

STANDARD DIABETIC DIET TABLES

TABLE 17

STANDARD DIABETIC DIETS FOR CHILDREN

Age in years.		3–5	6–8	9–11	12–16 I	12–16 II
		Gm.	Gm	Gm.	Gm.	Gm.
Vegetables	3%	200	300	400	400	400
Fruit	5%	200	200	100	100	
Fruit	10%	50	100	200	200	300
Cereal					14	14
Bread		45	60	60	60	60
Cream	20%		100	200	300	
Cream	40%					230
Milk		1000	900	800	700	700
Bacon			10	25	25	25
Eggs		1	1	1	2	2
Meat			50	50	50	75
Composition		Gm	Gm.	Gm	Gm	Gm.
Carbohydrate		95	111	119	130	127
Protein		45	62	67	75	75
Fat		47	76	99	122	158
Calories		980	1380	1640	1920	2230

For calories required add butter or equivalent

3–5 Calories	3–5 Butter	6–8 Calories	6–8 Butter	9–11 Calories	9–11 Butter	12–16 I Calories	12–16 I Butter	12–16 II Calories	12–16 II Butter
1140	20	1530	20	1790	20	2070	20	2540	40
1210	30	1610	30	1860	30	2150	30	2620	50
1290	40	1680	40	1940	40	2220	40	2690	60
1370	50	1760	50	2020	50	2300	50	2770	70
1440	60	1840	60	2090	60	2380	60	2850	80
1520	70	1910	70	2170	70	2450	70	2920	90
1600	80	1990	80	2250	80	2530	80	3000	100
		2060	90	2320	90	2610	90		
		2140	100	2400	100	2680	100		

... daily of cod liver oil or equivalent from October to April during first six years of life.

TABLE 18

STANDARD DIABETIC DIETS FOR ADULTS

		Diets for women.			Diets for men			
		I	II	III	I	II	III	IV
		Gm	Gm	Gm	Gm.	Gm	Gm.	Gm.
Vegetables	3%	400	400	400	400	400	400	400
Fruit	10%	400	400	400	400	400	400	300
Vegetables or fruits	20%	100	100	100	100	100	100	100
Cereal			14	14		14	14	20
Bread		60	80	80	60	80	80	120
Cream	20%	50	100	230	50	100	230	300
Milk			200	200		200	200	200
Milk, skimmed		300			400			
Bacon								15
Eggs		1	1	1	2	2	2	2
Meat		100	100	100	100	125	125	125
Composition.		Gm	Gm	Gm.	Gm	Gm.	Gm.	Gm
Carbohydrate		121	141	147	126	141	147	167
Protein		57	59	63	66	71	75	84
Fat		35	51	77	42	61	87	110
Calories		1030	1260	1530	1150	1400	1670	1990

For calories required add butter or equivalent.	Women I Calories	Women I Butter	Women II Calories	Women II Butter	Women III Calories	Women III Butter	Men I Calories	Men I Butter	Men II Calories	Men II Butter	Men III Calories	Men III Butter	Men IV Calories	Men IV Butter
	1260	30	1490	30	1920	50	1380	30	1780	50	2130	60	2450	60
	1330	40	1570	40	1990	60	1450	40	1860	60	2210	70	2530	70
	1410	50	1640	50	2070	70	1530	50	1930	70	2280	80	2610	80
	1490	60	1720	60	2150	80	1610	60	2010	80	2360	90	2680	90
			1800	70	2220	90	1680	70	2090	90			2760	100
			1870	80	2300	100	1760	80						

III

S.A.

2.9
2.8
2.7
2.6
2.5
2.4
2.3
2.2
2.1
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6

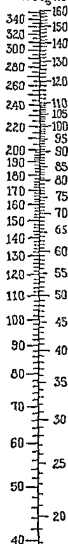
Surface area : square meters (DuBois)

Food Nomogram

Directions: The standards for age are arranged on the basis of the common method of expressing age as of the last birthday. To determine the desired calorie allowance, proceed as follows (1) Locate the weight on Scale I by means of a pin stuck through the erasor of a lead pencil. (2) Place the edge of the ruler against the pin and swing the other end of ruler to the patient's height on Scale II (3) Transfer the pin to the point where the ruler crosses Scale III which gives the surface area in sq meters (this value need not be read) (4) Holding the ruler against pin on the surface area scale, swing the left hand end of the ruler to the patient's standard for age and sex given on Scale IV (5) Transfer the pin to where the ruler now crosses Scale V which gives the basal heat production of the patient for 24 hours and represents the calories of food required by the fasting patient when resting in bed (basal calories) The calories necessary for activity bear a percentage relationship to those demanded for the resting condition. The so-called "white collar worker" when at work will need about 50 per cent more than his basal calories When activity is restricted, as in the hospital, the extra calories necessary will range from 10 to 30 per cent of the basal calories Therefore (6) estimate the per cent of calories above the basal and locate this point on Scale VI With the ruler connect this point with the point located previously on Scale V, and where the ruler now crosses Scale VII read the amount of food calories to be provided by the diet

I

Weight



W M Boothby and J Berkson
October 1933

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